EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/CHMP/501514/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0057

Marketing authorisation holder (MAH): Roche Registration Limited

Note

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

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
CRP	C-reactive protein
CSR	Clinical study report
DAS	Disease activity score
DMARD	Disease modifying anti-rheumatic drug
DMARD- IR	Inadequate responders to DMARD therapy
ESR	Erythrocyte sedimentation rate
HAQ-DI	Health assessment questionnaire disability index
IV	Intravenous
ITT	Intent-to-treat
NCI CTCAE	Common terminology criteria for adverse events of the National Cancer Institute
MAH	Marketing Authorization Holder
mTSS	van der Heijde modified total Sharp score
MTX	Methotrexate
PD	pharmacodynamics
PK	pharmacokinetic
PP	Per protocol
PY	Patient years
qw	Once per week
q4w	Every 4 weeks
RA	Rheumatoid arthritis
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SJC	Swollen joint counts
TCZ	Tocilizumab (RoActemra, Actemra)
TJC	Tender joint counts
TNF	Tumor necrosis factor
TNF-IR	Inadequate responders to anti-TNF therapy
ULN	Upper limit of normal
VAS	Visual analog 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 Limited submitted to the European Medicines Agency on 18 November 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) for the RoActemra subcutaneous formulation; as a consequence, section 4.1 of the SmPC is updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. Moreover, the updated RMP version 18 has been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0266/2015) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0266/2015) 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:

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

Timetable	Actual dates
Submission date	18 November 2015
Start of procedure:	3 January 2016
CHMP Co-Rapporteur Assessment Report	25 February 2016
CHMP Rapporteur Assessment Report	18 February 2016
PRAC Rapporteur Assessment Report	3 March 2016
PRAC Outcome	17 March 2016
CHMP members comments	N/A
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2016
Request for supplementary information (RSI)	1 April 2016
MAH responses to the Request for supplementary information	21 April 2016
Restart of the procedure	25 April 2016
CHMP Rapporteur Assessment Report	25 May 2016
PRAC Rapporteur Assessment Report	25 May 2016
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	9 June 2016
CHMP members comments	N/A
Updated CHMP Rapporteur Assessment Report	N/A
Opinion	23 June 2016

2. Scientific discussion

2.1. Introduction

Tocilizumab (TCZ) is a recombinant humanised anti-human IgG1 monoclonal antibody directed against the interleukin-6 receptor (IL-6R) that binds specifically to both soluble and membrane-bound IL-6R, thereby inhibiting IL-6-mediated signalling. TCZ is available in 2 different pharmaceutical forms to allow either administration by intravenous (IV) infusion or by subcutaneous (SC) injection.

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

The recommended dose for IV administration is 8 mg/kg TCZ every 4 weeks (q4w).

For SC administration, the recommended dose is 162 mg once every week (qw).

The IV formulation of TCZ is also approved in the EU, at the recommended dose, for the treatment of severe, active and progressive RA of ≤ 2 year duration, in adults not previously treated with MTX ("early RA"). This approval was based on the results of a dedicated pivotal Phase III trial (WA19926).

No dedicated study of the SC formulation of TCZ has been performed in adult RA patients (≤ 2 years duration) not previously treated with MTX (the early RA population). The purpose of this submission was to provide evidence to support extension of the currently approved early RA indication for the IV formulation to the SC formulation (162 mg qw starting dose) based on a comprehensive comparison of the efficacy and safety data from the relevant IV and SC pivotal Phase III trials used to support the current marketing authorizations.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP. A brief summary of available non-clinical data from previous applications is summarised in the following section.

2.2.1. Ecotoxicity / environmental risk assessment

Tocilizumab, is a recombinant humanised immunoglobulin IgG1 monoclonal antibody and in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) no environmental risk assessment studies were submitted in support of this application which was considered acceptable.

2.2.2. Conclusion on the non-clinical aspects

The currently available non-clinical data are sufficient to support the proposed indication with the SC tocilizumab formulation without any further amendments to the product information.

2.3. Clinical aspects

2.3.1. Introduction

No dedicated study of the SC formulation of TCZ has been performed in adult RA patients (< 2 years duration) not previously treated with MTX. The purpose of this submission was to provide evidence to support extension of the currently approved early RA indication for the IV formulation to the SC formulation (162 mg qw starting dose). Data from a subpopulation of patients enrolled in WA22762 (TCZ-SC and TCZ-IV) with a disease duration of ≤ 2 years and data from Study WA19926, which recruited adult patients with moderate to severe active early RA (≤ 2 years disease duration) who were naïve to treatment with both methotrexate (MTX) and a biologic agent were presented in support of this extension of indication.

Study WA19926 (FUNCTION) was the pivotal study to extend IV administration of TCZ to patient naïve to MTX, i.e. early RA patients and has been evaluated during EMEA/H/C/955/II/032 and EMEA/H/C/000955/II/0046.

Study WA22762 (Summacta) has been evaluated during EMEA/H/C/955/II/30 and was one of the two pivotal studies in the clinical development of TCZ for SC use (together with NA25220). The use of the SC formulation in monotherapy was further supported by the MRA229JP Phase III non-inferiority study which compared the SC and IV routes of administration in patients not receiving other DMARDs

The SC qw dose in the pivotal study WA22762 (comparing the SC and IV formulations) was shown to be non-inferior to the IV 8 mg/kg q4w dose in patients from the same study who were inadequate responders (IR) to disease modifying anti-rheumatic drugs (DMARDs) or to anti-tumour necrosis factor (TNF) therapy.

Studies NA25220 MRA229JP were considered supportive for this submission.

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.

- Tabular overview of clinical studies

Study no (phase)	Design & duration	Population	Patients randomized	Treatment
WA22762 (phase III)	Double-blind randomized, active controlled, non-inferiority study Randomized 1:1 Treatment for 24 weeks until 1°analysis. Re-randomization for 72-week open-label extension period: SC arm: 11:1 (SC:IV) IV arm: 2:1 (IV:SC)	Moderate to severe active RA (diagnosed ≥ 6 months) in patients with inadequate response to DMARDs that may have included one or more anti- TNFs (percentage of patients who failed one or more anti-TNFs was capped at ~20%) Subgroup of patients with RA diagnosis ≤ 2 years of first TCZ dose	Total 1262: A: **631** B: **631** Total 258: A: **131** B: **127**	A: **TCZ 162 mg SC qw+ Placebo IV q4w** B: **TCZ 8 mg/kg IV q4w+Placebo SC qw** A: **TCZ 162 mg SC qw+Placebo IV q4w** B: **TCZ 8 mg/kg IV q4w+Placebo SC qw** (All patients continued their background DMARD therapy during the study.)

WA19926 (phase III)	Double-blind, randomized placebo-controlled Randomized 1:1:1:1 1 analysis after 52 weeks of treatment. Double-blind long-term extension until Week 104	MTX-naïve patients with early (≤2 years since diagnosis), moderate to severe active RA	Total 1162: A: 291 B: 292 C: **290** D: 289	A: Placebo IV q4w+MTX 7.5 - 20 mg/wk B: TCZ 4 mg/kg IV q4w+MTX 7.5 - 20 mg/wk C: **TCZ 8 mg/kg IV q4w+MTX 7.5 - 20 mg/wk** D: TCZ 8 mg/kg IV q4w + placebo
SUPPORTIVE STUDIES				
NA25220 **(phase III)**	double-blind, randomized, placebo-controlled superiority study Randomized 2:1 (TCZ SC vs. placebo SC) Treatment for 24 weeks Re-randomized for 72 weeks open-label extension period: TCZ arm: 1:1 placebo arm: 1:1	Moderate to severe active RA in patients with inadequate response to DMARDs that may have included one or more anti-TNFs (percentage of patients who failed one or more anti-TNFs was capped at ~20%)	Total 656: A: 437 B: 219	A: TCZ 162 mg SC q2w + DMARD B: placebo SC q2w + DMARD
MRA229JP **(phase III)**	double-blind, randomized, active-controlled non-inferiority study	RA patients with inadequate response to DMARDS, including one or more anti-TNFs	Total 348 A: 174 B: 174	A: TCZ 162 mg SC q2w (PFS) B: TCZ: 8 mg/kg IV q4w

2.3.2. Pharmacokinetics

Table 1. Summary of clinical trials contributing to the clinical pharmacology summary

Study No.	Study Design	Patient Population	Treatment Regimen
WA19926	4-arm, double-blind, randomized, placebo-controlled Duration: 104 weeks	Early RA (≤ 2 years) Moderate to severe active RA Naïve to MTX or biologic agents	Placebo IV q4w + MTX or TCZ IV q4w 4 mg/kg + MTX or TCZ IV q4w 8 mg/kg + MTX or TCZ IV q4w 8 mg/kg + placebo
WA22762	2-arm, double-blind, randomized, active-controlled Duration: 97 weeks	DMARD-IR Moderate to severe active RA with inadequate response to DMARDs	TCZ IV q4w 8 mg/kg + MTX or TCZ SC qw 162 mg + MTX

As the results of these studies have been previously evaluated, only a brief outline of the results is presented in this report.

- **Study WA2276**

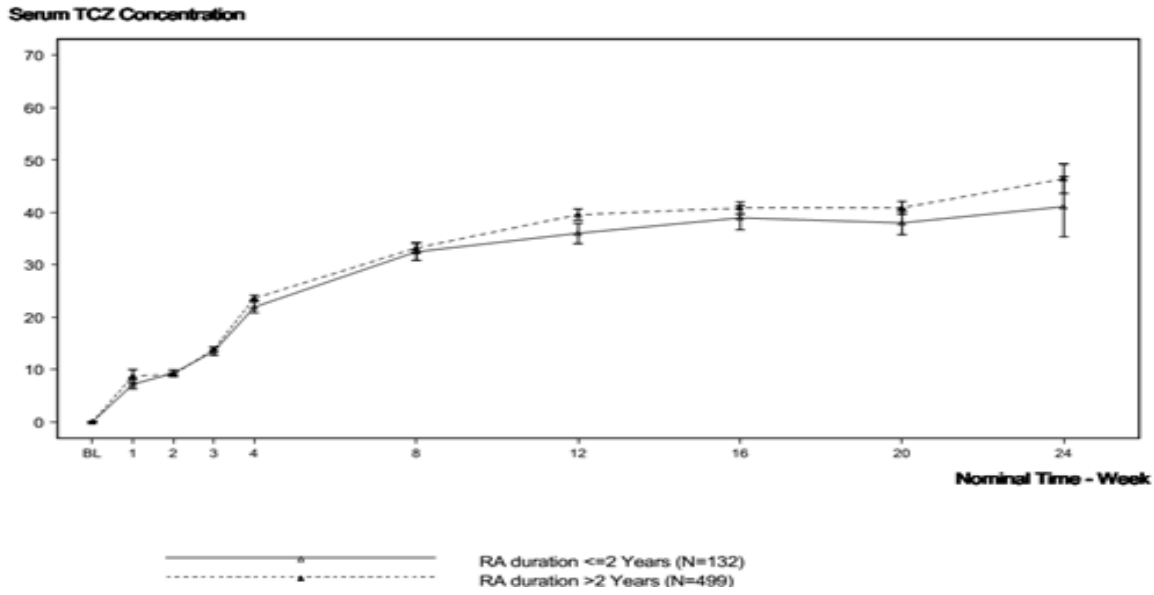
Results up to Week 24 (double-blind study period) demonstrated that the PD responses, of 8 mg/kg TCZ administered IV every 4 weeks were comparable to those following 162 mg TCZ administered SC on a weekly basis (for further details please refer to the EPAR for EMEA/H/C/000955/X/0030.

- **Study WA19926**

Results demonstrated that TCZ exposures and PD responses in early RA patients following q4w IV infusions of TCZ at 4 mg/kg and 8 mg/kg (with or without concomitant MTX) were comparable to those previously seen in RA patients who failed previous with anti-TNFs or other DMARDS (for further details please refer to the EPAR EMEA/H/C/955/II/032).

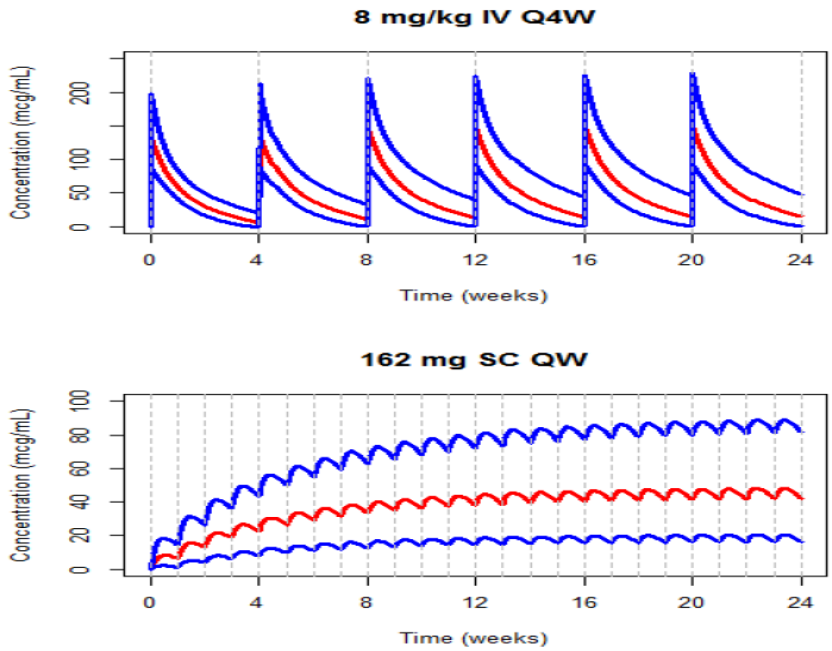
As a subset of adult RA patients (132 out of 631 total) from the SC treated arm of WA22762 had been diagnosed with RA within 2 years or less at the time they entered that study, TCZ exposures in patients from WA22762 treated with 162 mg SC TCZ every week were analysed based on disease duration at time of study. The TCZ concentration-time profiles up to Week 24 (end of the randomized, double-blind study period) in early RA patients (who entered the study with RA duration of 2 years or less) versus patients who entered the study more than 2 years following RA diagnosis are depicted in **Figure 1**.

Figure 1. Mean (± SE) TCZ Concentrations for WA22762 SC-Treated Patients by RA Duration



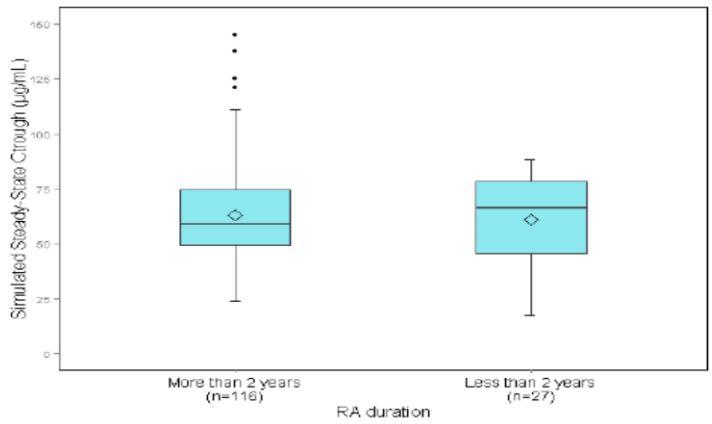
From a previously submitted population PK (evaluated during EMEA/H/C/000955/X/0030), the complete time-courses of tocilizumab serum concentrations following 24 weeks of 8 mg/kg Q4W IV or 162 mg QW SC treatment was simulated and are displayed in **Figure 2.**

Figure 2. Simulated time-course of tocilizumab serum concentrations over 4 months of treatment: Median (red) and 90% prediction intervals (blue) of the simulated concentration-time profiles. For each dosing regimen concentrations were simulated every 12 h and at 1 hour after each dose for 5000 patients with the covariate values sampled with replacement from the analysis population.



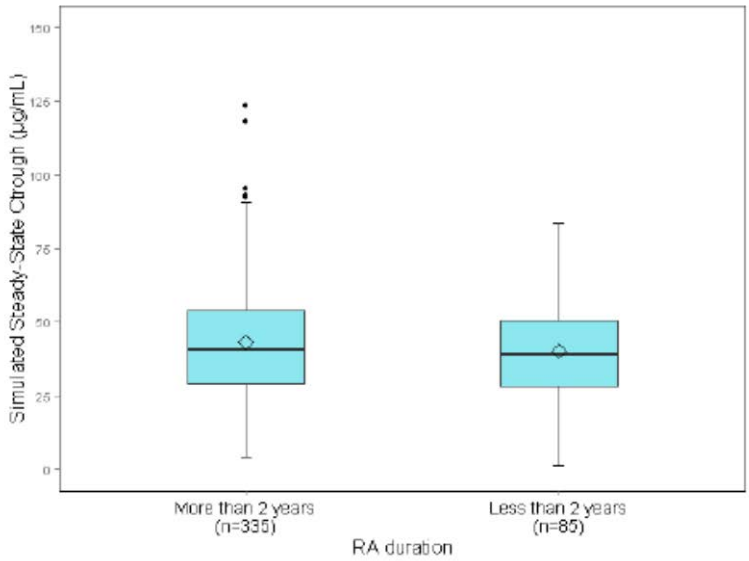
Simulated steady-state TCZ exposures between patients with different disease duration from study WA22762 TCZ, following weekly SC dosing by (baseline) body weight category are presented in **Figures 3-5.**

Figure 3. Simulated steady-state $C_{[trough]}$ for WA22762 TCZ SC-treated patients by RA duration (body weight < 60 kg)



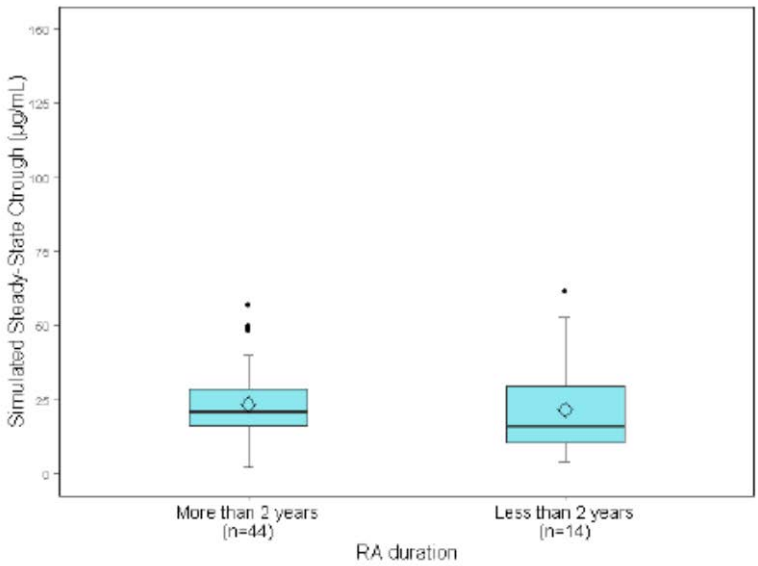
Upper hinge = 75th percentile; line inside box = median; diamond = mean; lower hinge = 25th percentile; endpoint of upper whisker = 1.5 × inter-quartile range (IQR) + upper hinge; endpoint of lower whisker = lower hinge -1.5 × IQR.

Figure 4. Simulated steady-state $C_{[trough]}$ for WA22762 TCZ SC-treated patients by RA duration (body weight 60 - 100 kg)



Upper hinge = 75th percentile; line inside box = median; diamond = mean; lower hinge = 25th percentile; endpoint of upper whisker = 1.5 × inter-quartile range (IQR) + upper hinge; endpoint of lower whisker = lower hinge -1.5 × IQR.

Figure 5. Simulated steady-state $C_{[trough]}$ for WA22762 TCZ SC-treated patients by RA Duration (body Weight > 100 kg)



Upper hinge = 75th percentile; line inside box = median; diamond = mean; lower hinge = 25th percentile; endpoint of upper whisker = 1.5 × inter-quartile range (IQR) + upper hinge; endpoint of lower whisker = lower hinge -1.5 × IQR.

2.3.3. Discussion on clinical pharmacology

Although no formal study has been conducted employing SC TCZ in early RA patients, a subset of adult RA patients from the SC treated arm of Study WA22762 had been diagnosed with RA within 2 years or less at the time they entered that study. TCZ exposures following weekly SC dosing up to Week 24 were overall comparable in both groups, and unaffected by duration of disease diagnosis. Therefore a similar saturation of the target (IL-6 receptors) can be expected to occur in early RA patients following weekly SC dosing with 162 mg TCZ as had been observed in RA patients with a longer history of diagnosis and treated with the same regimen.

Exposure is also comparable when examining exposure subset by three body categories (< 60, 60 - 100, > 100 kg) in patients with $\leq$ 2 years disease duration versus those with disease of longer standing. The simulated steady-state $C_{[trough]}$ values are based upon previously submitted population PK analyses with the assumption that all patients received their protocol specified doses.

Despite the small sample sizes in some subgroups in this analysis (i.e., n =14 for disease duration of $\leq$2 years and baseline body weight > 100 kg) the results are consistent across all subgroups indicating that the effect of body weight in the bioavailability of tocilizumab would be similar between patients in early RA and the RA population with disease of longer standing.

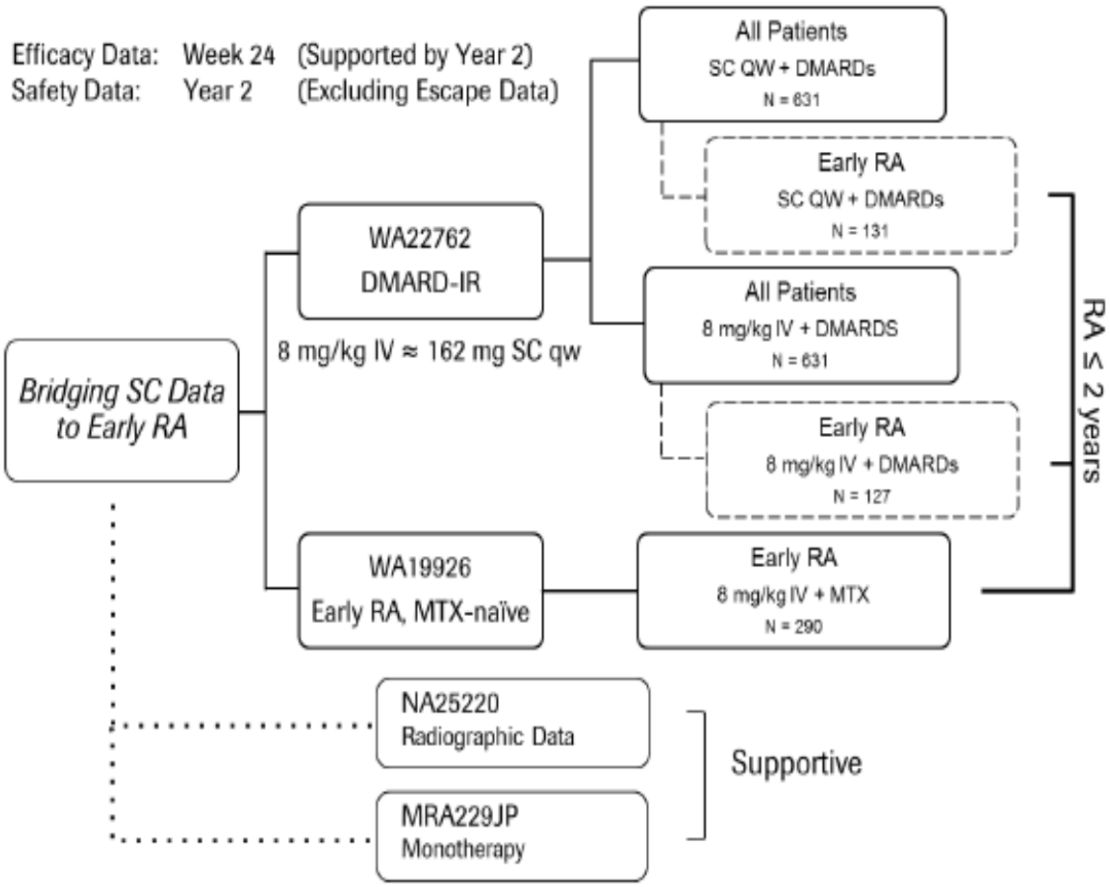
2.3.4. Conclusions on clinical pharmacology

The comparable exposures and PD responses, between early RA patients and RA patients with no disease duration specified which has previously been established following IV administration to can be expected to apply to the same extent following SC administration of TCZ.

2.4. Clinical efficacy

No dedicated study has been conducted with the SC TCZ formulation in a patient population with early RA. This submission provides a bridge between the data from different patient groups of the pivotal SC and IV studies, in order to demonstrate that SC or IV administration of TCZ leads to comparable efficacy and safety results in patients with early RA. The overall bridging study employed to do this is depicted in **Figure 6**.

Figure 6. Overall bridging strategy



Based on the comparable observed efficacy and safety, Study WA22762 demonstrated that TCZ 162 mg SC qw is the best matching dose to TCZ IV 8 mg/kg q4w to treat adult RA patients with inadequate responses to traditional DMARDs. The regimen of TCZ IV 8 mg/kg q4w has been approved for the treatment of early RA patients based on the results of Study WA19926.

Efficacy data presented focus on the Week 24 analyses when the majority of endpoints from the double-blind periods in both studies were assessed, and before patients in Study WA22762 may have been reassigned to a different treatment modality at the Week 24 re-randomization.

Furthermore, the maintenance of efficacy over the entire 2-year study duration was also investigated. The analyses are supplemented by radiographic data from the NA25220 study and by the data from TCZ-SC therapy in a monotherapy setting in study MRA229JP.

2.4.1. Main studies

Table 2. Summary of pivotal studies contributing to efficacy evaluation at Week 24

Study No. (Phase)	Design and Duration	Population	Patients Randomized	Treatment
WA22762 (Phase III)	Double-blind, randomized, active controlled, non-inferiority study Randomized 1:1 Treatment for 24 weeks until 1*analysis. Re-randomization for 72-week open-label extension period: SC arm: 11:1 (SC:IV) IV arm: 2:1 (IV:SC)	Moderate to severe active RA (diagnosed ≥6 months) in patients with inadequate response to DMARDs that may have included one or more anti-TNFs (percentage of patients who failed one or more anti-TNFs was capped at ~20%) Subgroup of patients with RA diagnosis ≤2 years of first TCZ dose	Total 1262: A: **631** B: **631** Total 258: A: **131** B: **127**	A: **TCZ 162 mg SC qw+Placebo IV q4w** B: **TCZ 8 mg/kg IV q4w+Placebo SC qw** A: **TCZ 162 mg SC qw+Placebo IV q4w** B: **TCZ 8 mg/kg IV q4w+Placebo SC qw** (All patients continued their background DMARD therapy during the study.)
WA19926 (Phase III)	Double-blind, randomized, placebo-controlled Randomized 1:1:1:1 1 analysis after 52 weeks of treatment. Double-blind long-term extension until Week 104	MTX-naïve patients with early (≤2 years since diagnosis), moderate to severe active RA	Total 1162: A: 291 B: 292 C: **290** D: 289	A: Placebo IV q4w + MTX 7.5–20 mg/wk B: TCZ 4 mg/kg IV q4w + MTX 7.5–20 mg/wk C: **TCZ 8 mg/kg IV q4w + MTX 7.5–20 mg/wk** D: TCZ 8 mg/kg IV q4w + placebo

Note: Treatment groups used for the primary data presentations in this Summary of Clinical Efficacy are indicated in **bold**.

Study Participants

The patient populations in the WA22762 and WA19926 studies both consisted of patients with moderate to severe active RA.

The main difference between the WA22762 and WA19926 patient populations was that the former had to have an inadequate clinical response to a stable dose of DMARD therapy that may have included one or more anti-TNFs (with the percentage of patients who had failed one or more TNF antagonists being capped at approximately 20%). On the other hand, the early RA population of study WA19926 included only MTX-naïve patients with baseline RA duration of ≤ 2 years. To ensure that this was also a population with active and progressive RA disease, the selection criteria enriched for patients with high disease activity score, serologic positivity and/or joint erosions.

The population in the supporting study NA25220 was very similar to that of the 2 pivotal studies and the patient selection criteria essentially followed those used for WA22762.

Key inclusion and exclusion criteria in the pivotal studies are summarised in **Tables 3** and **4**.

Table 3. Key inclusion criteria for studies contributing to efficacy evaluation

Inclusion Criteria:	WA22762	WA19926
RA Duration (ACR Criteria)		
≥ 6 months	●	
≤ 2 years		●
DAS28 Score		
> 3.2	n/s	●
Joint Counts		
SJC ≥ 4 (of 66) and TJC ≥ 4 (of 68)	●	
SJC ≥ 4 (of 66) and TJC ≥ 6 (of 68)		●
Acute Phase Reactants		
CRP ≥ 1 mg/dL (10 mg/L) or ESR ≥ 28 mm/h	●	●
Other RA Disease Features		
Positive Rheumatoid Factor or Anti-CCP Ab, or if negative for both: radiographic evidence of ≥ 1 erosion of hands, wrists or feet (determined by central reading)	n/s	●
MTX		
MTX naïve		●
Other DMARDs		
DMARD, which had been at a stable dose for at least 8 weeks prior to baseline. Biologics discontinued prior to randomization (etanercept for ≥ 2 weeks, infliximab, certolizumab, golimumab, abatacept, or adalimumab for ≥ 8 weeks, or anakinra for ≥ 1 week)	●	
All previous DMARDs withdrawn		●
Previous NSAIDs/Oral Corticosteroids		
Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) if dose had been stable for at least 4 weeks prior to baseline; NSAIDs if the dose had been stable for at least 2 weeks prior to baseline		●
Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDS (up to the maximum recommended dose) permitted if the dose had been stable for at least 4 weeks prior to baseline	●	

Table 4. Key exclusion criteria for studies contributing to efficacy evaluation

Exclusion Criteria:	WA22762	WA19926
Functional class IV RA (as defined by ACR Classification of Functional Status in RA)	●	●
Excluded Previous or Concomitant Therapy		
Prior treatment with any biologic agent		●
Intra-articular or parenteral corticosteroids within 6 weeks prior to screening		●
Intra-articular or parenteral corticosteroids within 4 weeks prior to screening	●	

Abbreviations: ACR = American College of Rheumatology, CRP = C-reactive protein, DAS2 = Disease Activity Score 28, DMARD = disease- modifying antirheumatic drug, ESR = erythrocyte sedimentation rate, IV = intravenous, n/s = not specified, MTX = methotrexate, NSAID = non-steroidal antiinflammatory drug, RA = rheumatoid arthritis, SJ = swollen joint count, TCZ = tocilizumab, TJC = tender joint count, TNF = tumor necrosis factor.

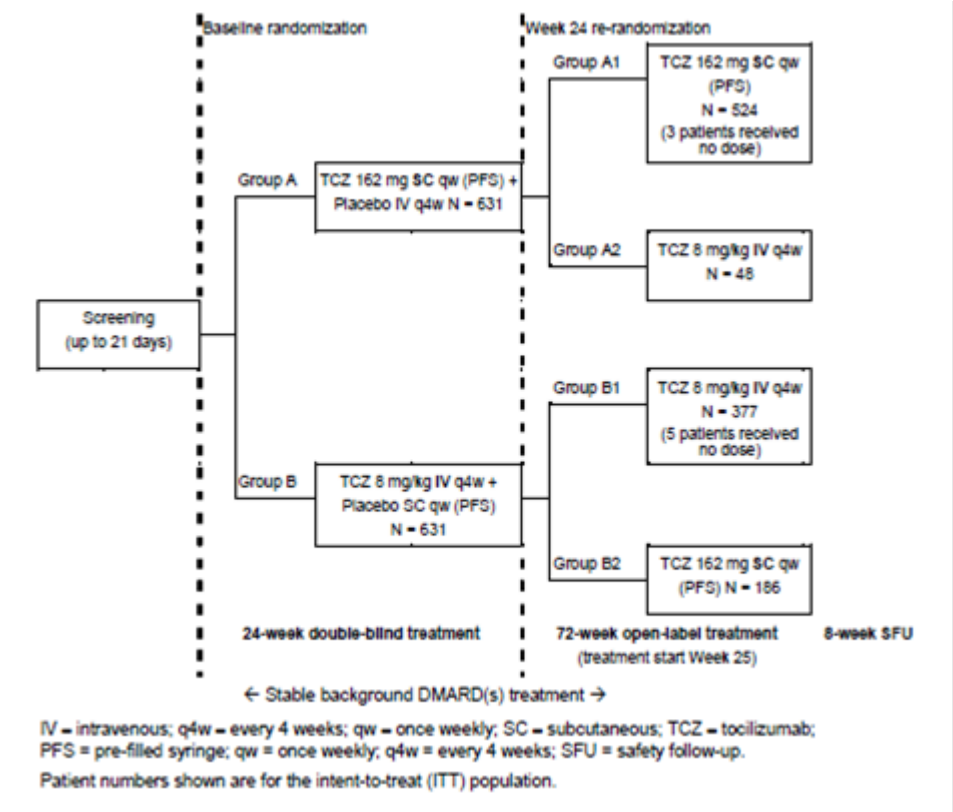
Treatments

Study WA2276

The patients were randomized (631 patients in each group) to the following blinded treatments for 24 weeks:

- TCZ 162 mg SC qw + placebo IV q4w
- TCZ 8 mg/kg IV q4w + placebo SC qw

Figure 7. Design of Study WA22762



IV = intravenous; q4w = every 4 weeks; qw = once weekly; SC = subcutaneous; TCZ = tocilizumab; PFS = pre-filled syringe; qw = once weekly; q4w = every 4 weeks; SFU = safety follow-up.

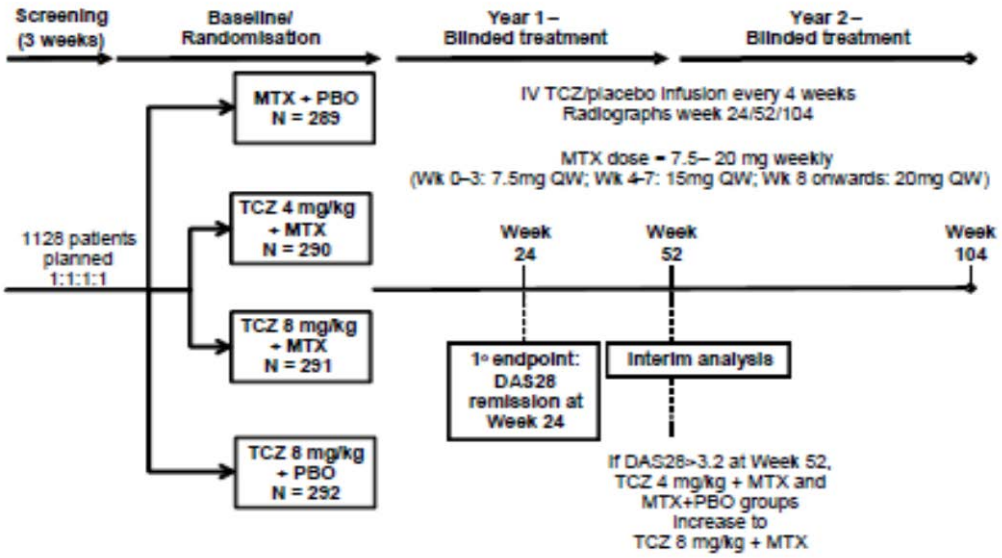
Patient numbers shown are for the intent-to-treat (ITT) population.

Study WA19926

Patients were randomized to the following treatment arms:

- Placebo IV q4w + MTX
- TCZ 4 mg/kg IV q4w + MTX
- TCZ 8 mg/kg IV q4w + MTX
- TCZ 8 mg/kg IV q4w + Placebo

Figure 8. Design of Study WA19926



Concomitant medication

DMARDs

Patients in the WA22762 had to receive background therapy with at least one permitted non-biologic DMARD (azathioprine, chloroquine, hydroxychloroquine, leflunomide, methotrexate or sulfasalazine) at a stable dose at least 8 weeks prior to baseline and throughout the study. DMARDs could be used alone or in combination, except for the combination of methotrexate and leflunomide. DMARDs were to remain stable, but dose reduction was permitted for safety reasons.

In WA19926, DMARD use was prohibited during the study.

Corticosteroids / NSAIDS

Oral corticosteroids for RA (≤ 10 mg/day of prednisone or equivalent) were allowed in Study WA22762 and Study WA19926 if the dose had been stable for more than 4 weeks prior to baseline. Oral NSAIDs were permitted if the dose was stable for at least 2 weeks before baseline in Study WA19226 and for more than 4 weeks in WA22762.

Analgesics other than NSAIDs were permitted for pain management as required (but were not to be taken within 12 hours prior to a study visit).

Intravenous and intramuscular corticosteroids were not permitted during the study.

Injection of intra-articular corticosteroids during the double-blind treatment periods of the studies was discouraged, but could be used in a limited fashion. No more than one joint per 24-week period in WA22762, or 2 joints per 52-week period in WA19226. No single injection could exceed 40 mg of triamcinolone (or equivalent).

All patients who received MTX (or the corresponding placebo) received folic acid or equivalent at a dose of ≥ 5 mg/week or equivalent. Use of lipid-lowering agents in patients with elevated lipids was strongly encouraged any time during the study.

Outcomes / endpoints

Study WA22752

The primary endpoint was to demonstrate the non-inferiority of TCZ SC versus TCZ IV with respect to the

American College of Rheumatology 20% improvement (ACR20) response rate at Week 24.

Secondary endpoints included: ACR50/70 (ACR50 and ACR70 responses reflect a 50% and a 70% improvement from baseline), the proportion of patients achieving a DAS28 ≤ 2.6 (remission) and the proportion of patients achieving a HAQ-DI ≥ 0.3.

Study WA19926

The primary endpoint of the study was the proportion of patients who achieve DAS28 remission (DAS28 ≤ 2.6) at 24 weeks.

Secondary endpoints included ACR20/50/70, DAS28 < 2.6 (remission) and HAQ-DI decrease ≥ 0.3 since baseline, and change from baseline in mTSS, at 24 and 52 weeks, and maintenance of efficacy effects up to 24 months.

Statistical methods

This submission presents an evaluation and comparison of data between studies and includes unplanned analyses of subpopulations. In study WA22762, a post hoc subpopulation of patients with RA < 2 years was provided, although the patients were not stratified at the time of randomization for the duration of RA. This sub population makes up approximately 20% of the All Patient population. There were differences between patient populations in studies WA22762 and WA19926 regarding previous exposure to biologic and non-biologic DMARDS. Additionally, the numbers of patients contributing to efficacy and safety data varied between treatment groups and studies.

Table 5. Analysis types and populations presented in Clinical Study Reports and in the comparisons across Studies

	WA22762 CSR	WA19926 CSR	Comparison across Studies in this SCE
Week 24 Analyses:			
Primary endpoint	ACR 20	DAS28 remission (DAS28<2.6)	Informal comparison between several endpoints, including ACR20 and DAS28 remission
Population for analysis of 1° endpoint	Per Protocol	Intent-to-Treat	Intent-to-Treat
Analysis type	Non-responder	Non-responder	Non-responder
Year 2 Analyses:			
"Year 2" time point	97 weeks	104 weeks	"2 years"
Population for analysis	Intent-to-Treat	Intent-to-Treat	Intent-to-Treat
Analysis type	Completer	Non-responder	Non-responder

Comparison of study design

Both Studies WA19926 and WA22762 were double blind, active controlled studies with a primary endpoint at Week 24. Both studies include the treatment arm TCZ 8 mg/kg IV + DMARD administered every 4 weeks. In Study WA22762, this was given while patients remained on a background non-biologic DMARD (approx. 80% patients received MTX), whilst in study Study WA19926 all patients not randomized to monotherapy TCZ, received TCZ in combination with MTX, which was initiated at study start. Both studies used the same outcome measures (e.g. DAS28, ACR response) and utilized the same data collection instruments (e.g. HAQ-DI).

Both studies recruited patients with moderate to severe active RA. In Study WA22762 patients must have had an inadequate response to a stable dose of DMARDs, whereas in Study WA19926 patients must have been naïve to MTX/ biologic agents.

Study WA22762 and Study WA19926 were conducted independently from each other and without intent to directly compare the efficacy and safety outcomes.

The patient population in both studies was similar apart from the shorter disease duration and the requirement to be naïve to DMARDs in WA19926.

Both studies assessed similar efficacy endpoints (the primary endpoint in each study was a key secondary endpoint in the other study) and safety data were collected in a similar fashion across both studies.

The efficacy analyses presented in this submission apply the same data handling rules to facilitate comparison across studies and the data have also been analysed for the subset of Study WA22762 patients with similar disease duration as the Study WA19926 patients.

Results

Baseline data

Table 6. Baseline demographic and disease characteristics (Safety Populations during 24-Week study period)

	WA22762				WA19926
	All Patients		Patients with RA≤2 Years		
	TCZ 162 mg SC qw+DMARD n=631	TCZ 8 mg/kg IV q4w+DMARD n=631	TCZ 162 mg SC qw+DMARD n=131	TCZ 8 mg/kg IV q4w+DMARD n=127	TCZ 8 mg/kg IV q4w + MTX N = 290
Baseline Demographic Characteristics					
Female, n (%)	520 (82%)	521 (83%)	103 (79%)	98 (77%)	228 (79%)
Caucasian, n (%)	486 (77%)	479 (76%)	98 (75%)	92 (72%)	229 (79%)
Age, years					
Mean (± SD)	53 (12.4)	53 (12.5)	50.4 (14.0)	49.1 (14.4)	49.5 (13.7)
Range	18 – 83	18 – 86	18 – 83	21 – 86	18 – 79
Body weight, kg					
Mean (± SD)	75 (19.1)	74 (19.0)	77 (21.6)	77 (19.2)	75 (19.3)
Range	38 – 150	32 – 150	40 – 150	42 – 141	42 – 150
Baseline Disease Characteristics: Mean (± SD)					
RA duration, years					
Mean (± SD)	8.7 (8.3)	8.6 (8.1)	1.2 (0.4)	1.1 (0.4)	0.5 (0.5)
Median	5.8	6.2	1.1	1.0	0.3
DAS28	6.6 (1.0)	6.7 (1.0)	6.6 (1.1)	6.8 (1.0)	6.7 (1.1)
HAQ-DI	1.6 (0.6)	1.7 (0.6)	1.5 (0.7)	1.6 (0.7)	1.5 (0.6)
No. of previous DMARDs	1.4 (0.7)	1.4 (0.7)	1.4 (0.6)	1.5 (0.6)	0.2 (0.5)
Oral corticosteroids, n (%)	344 (55%)	338 (54%)	73 (55%)	66 (52%)	95 (33%)
TNF-IR, n (%)	142 (22%)	136 (22%)	11 (8%)	10 (8%)	0 (0%)

Outcomes and estimation

Table 7. Comparison of key efficacy parameters at Week 24: Study WA22762 all patients and patients with RA ≤ 2 Years, and StudyWA19926 (ITT Population)

	WA22762				WA19926
	All Patients		Early RA Patients (RA≤2 years)		
	TCZ 162 mg SC qw + DMARD N=631	TCZ 8 mg/kg IV q4w + DMARD N=631	TCZ 162 mg SC qw + DMARD N=132 [a]	TCZ 8 mg/kg IV q4w + DMARD N=127	TCZ 8 mg/kg IV q4w + MTX N=290
ACR20, n (%)	427 (67.7) [a]	443 (70.2) [a]	90 (68.2) [a]	97 (76.4) [a]	216 (74.5)
ACR50, n (%)	287 (45.5)	294 (46.6)	62 (47.0)	74 (58.3)	165 (56.9)
ACR70, n (%)	149 (23.6)	167 (26.5)	37 (28.0)	42 (33.1)	112 (38.6)
DAS28 < 2.6, Remission, n (%) [c]	217 (34.4)	205 (32.5)	47 (35.6)	49 (38.6)	130 (44.8) [b]
DAS28 < 3.2, Low Disease Activity, n (%) [c]	312 (49.4)	289 (45.8)	63 (47.7)	63 (49.6)	167 (57.6)
HAQ-DI decrease ≥ 0.3, n (%) [d]	379 (66.3)	379 (66.8)	80 (69.0)	95 (84.1)	196 (78.4)

[a] Robustness analysis of primary endpoint using ITT population for WA22762, at Week 24. Primary analysis was conducted on Per-protocol Population

[b] Primary endpoint for WA19926, at Week 24

[c] Percentages for WA22762 are manually calculated using N as the denominator to align with the non-responder imputation used in WA19926

[d] Percentages calculated using number of observations available

Table 8. Comparison of key efficacy parameters at Year 2: WA22762 all patients and patients with RA ≤ 2 Years, and WA19926 (ITT Population)

	WA22762				WA19926
	All Patients		Early RA Patients (RA≤2 years)		
	TCZ 162 mg SC qw + DMARD N=521	TCZ 8 mg/kg IV q4w + DMARD N=372	TCZ 162 mg SC qw + DMARD N=107	TCZ 8 mg/kg IV q4w + DMARD N=75	TCZ 8 mg/kg IV q4w + MTX N=290
ACR20, n (%) [a]	377 (72.4)	264 (71.0)	77 (72.0)	53 (70.7)	189 (65.2)
ACR50, n (%) [a]	295 (56.6)	198 (53.2)	69 (64.5)	41 (54.7)	167 (57.6)
ACR70, n (%) [a]	202 (38.8)	133 (35.8)	51 (47.7)	28 (37.3)	135 (46.6)
DAS28 < 2.6, Remission, n (%) [a]	238 (45.7)	142 (38.2)	57 (53.3)	34 (45.3)	138 (47.6)
DAS28 < 3.2, Low Disease Activity, n (%) [a]	299 (57.4)	188 (50.5)	67 (62.6)	39 (52.0)	161 (55.5)
HAQ-DI decrease ≥ 0.3, n (%) [b]	322 (72.4)	219 (69.1)	67 (72.8)	49 (83.1)	171 (83.4)

[a] Percentages calculated based on non-responder imputation.

[b] Percentages calculated using number of observations available.

A similar analysis was submitted for Study WA22762, comparing patients with a diagnosis RA ≤2 Years to those with a diagnosis of >2 years. The results of this analysis for the efficacy parameters evaluated at week 24 are shown in **Table 9**.

Table 9. Comparison of key efficacy parameters at Week 24: WA22762 patients with RA > 2 years and patients with RA ≤ 2 Years (ITT Population)

	Patients with RA>2 Years		Patients with RA≤2 Years		All Patients	
	TCZ 162 mg SC qw + DMARD N = 499	TCZ 8 mg/kg IV q4w + DMARD N = 504	TCZ 162 mg SC qw+DMARD N=132	TCZ 8 mg/kg IV q4w+DMARD N=127	TCZ 162 mg SC qw+DMARD N=631	TCZ 8 mg/kg IV q4w+DMARD N=631
ACR20, n (%)	337 (67.5) [a]	346 (68.7) [a]	90 (68.2) [a]	97 (76.4) [a]	427 (67.7) [a]	443 (70.2) [a]
ACR50, n (%)	225 (45.1)	220 (43.7)	62 (47.0)	74 (58.3)	287 (45.5)	294 (46.6)
ACR70, n (%)	112 (22.4)	125 (24.8)	37 (28.0)	42 (33.1)	149 (23.6)	167 (26.5)
DAS28 < 2.6, Remission, n (%) [b]	170 (34.1)	156 (31.0)	47 (35.6)	49 (38.6)	217 (34.4)	205 (32.5)
DAS28 < 3.2, Low Disease Activity, n (%) [b]	249 (49.9)	226 (44.8)	63 (47.7)	63 (49.6)	312 (49.4)	289 (45.8)
HAQ-DI decrease ≥ 0.3, n (%) [c]	299 (65.6)	284 (62.6)	80 (69.0)	95 (84.1)	379 (66.3)	379 (66.8)

[a] Robustness analysis of primary endpoint using ITT population for WA22762, at Week 24. Primary analysis was conducted on Per-protocol Population

[b] To allow comparability across studies, the percentages for DAS28 data for WA22762 have been re-calculated using a non-responder approach (i.e, using N as the denominator). The DAS28 data may thus differ slightly from those presented in the corresponding study report

[c] Percentages calculated using number of observations available

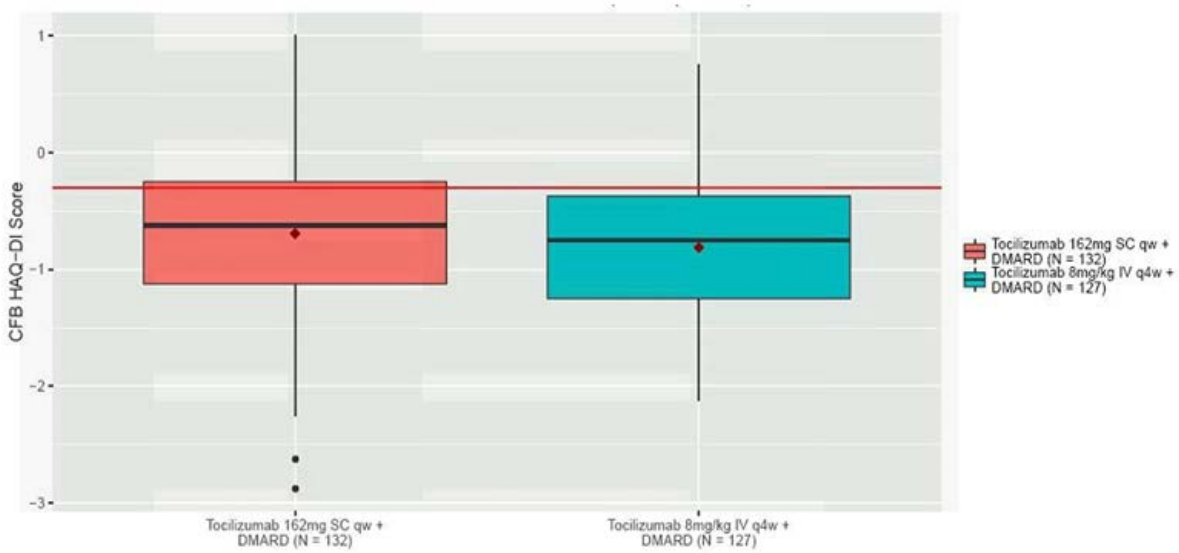
To evaluate any potential differences between the IV and SC administration of TCZ, in the early phases of treatment, the key efficacy parameters were also analysed between Weeks 4-20 (**Table 10**).

Table 10. Key Efficacy Parameters Over Time: WA22762 (ITT Population)

	Patients with RA>2 Years		Patients with RA≤2 Years		All Patients	
	TCZ 162 mg SC qw + DMARD N = 499	TCZ 8 mg/kg IV q4w + DMARD N = 504	TCZ 162 mg SC qw+DMARD N=132 [c]	TCZ 8 mg/kg IV q4w+DMARD N=127	TCZ 162 mg SC qw+DMARD N=631	TCZ 8 mg/kg IV q4w+DMARD N=631
Week 4						
ACR20, n (%)	222 (44.5)	239 (47.4)	74 (56.1)	68 (53.5)	296 (46.9)	307 (48.7)
ACR50, n (%)	79 (15.8)	75 (14.9)	23 (17.4)	23 (18.1)	102 (16.2)	98 (15.5)
ACR70, n (%)	30 (6.0)	25 (5.0)	8 (6.1)	8 (6.3)	38 (6.0)	33 (5.2)
DAS28 < 2.6, Remission, n (%) [a]	48 (9.6)	37 (7.3)	17 (12.9)	15 (11.8)	65 (10.3)	52 (8.2)
DAS28 < 3.2, Low Disease Activity, n (%) [a]	93 (18.6)	83 (16.5)	34 (25.8)	26 (20.5)	127 (20.1)	109 (17.3)
HAQ-DI decrease ≥ 0.3, n (%) [b]	212 (43.6)	219 (44.2)	63 (49.6)	65 (52.4)	275 (44.9)	284 (45.9)
Week 12						
ACR20, n (%)	337 (67.5)	331 (65.7)	87 (65.9)	86 (67.7)	424 (67.2)	417 (66.1)
ACR50, n (%)	184 (36.9)	185 (36.7)	54 (40.9)	52 (40.9)	238 (37.7)	237 (37.6)
ACR70, n (%)	84 (16.8)	85 (16.9)	25 (18.9)	30 (23.6)	109 (17.3)	115 (18.2)
DAS28 < 2.6, Remission, n (%) [a]	143 (28.7)	135 (26.8)	44 (33.3)	36 (28.3)	187 (29.6)	171 (27.1)
DAS28 < 3.2, Low Disease Activity, n (%) [a]	210 (42.1)	192 (38.1)	61 (46.2)	53 (41.7)	271 (42.9)	245 (38.8)
HAQ-DI decrease ≥ 0.3, n (%) [b]	290 (61.3)	271 (56.9)	80 (65.0)	83 (68.6)	370 (62.1)	354 (59.3)
Week 20						
ACR20, n (%)	339 (67.9)	347 (68.8)	90 (68.2)	92 (72.4)	429 (68.0)	439 (69.6)
ACR50, n (%)	220 (44.1)	224 (44.4)	62 (47.0)	67 (52.8)	282 (44.7)	291 (46.1)
ACR70, n (%)	115 (23.0)	121 (24.0)	35 (26.5)	43 (33.9)	150 (23.8)	164 (26.0)
DAS28 < 2.6, Remission, n (%) [a]	165 (35.9)	163 (35.6)	49 (37.1)	41 (32.3)	214 (37.1)	204 (35.7)
DAS28 < 3.2, Low Disease Activity, n (%) [a]	238 (51.7)	225 (49.1)	59 (44.7)	61 (48.0)	297 (51.5)	286 (50.1)
HAQ-DI decrease ≥ 0.3, n (%) [b]	289 (62.4)	290 (62.9)	81 (69.2)	86 (74.1)	370 (63.8)	376 (65.2)

The distribution of HAQ-DI scores at the Week 24 visit was investigated in relation to the chosen -0.3 cut-off used as the endpoint in the original analysis of Study WA22762 (**Figure 8**).

Figure 9. Box-Plot of Change in HAQ-DI Score from Baseline at Week 24 in WA22762 Early RA Patients



Supportive studies

Radiographic endpoints in Study WA19926 and Study NA25220

Study NA25220 was a Phase III, superiority, two-arm randomized, double-blind, placebo-controlled, parallel group, international, multi-centre study in patients with moderate to severe active RA who had an inadequate response to current DMARD therapy including one or more anti-TNF biologic agents (TNF-IRs limited to 20% of the patients).

Eligible patients were randomized in a 2:1 ratio to treatment with either TCZ 162 mg SC q2w or placebo SC q2w for 24 weeks, in combination with non-biologic DMARDs. In the 24-week double-blind period, a PFS was used for study drug administration. At Week 24, patients were re-randomized to open-label treatment with TCZ 162 mg SC q2w + DMARD. Radiographic images of hands and feet were taken at screening, Week 24, and Week 48.

The population in the supporting Study NA25220 was very similar to that of the 2 pivotal studies and the patient selection criteria essentially followed those used for Study WA22762. The van der Heijde modified Total Sharp Score (mTSS) from these studies are presented in **Table 11**.

Table 11. Change from baseline in mTSS at Week 24 (WA19926 and NA25220 ITT Populations) –Linear e Extrapolation Method

	WA19926: ALL PATIENTS				NA25220: ALL PATIENTS	
	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)	TCZ PFS q2w (N = 437)	Placebo PFS q2w (N = 219)
Modified Total SharpScore						
Baseline						
N	286	287	288	292	391	186
Mean	5.66	7.72	6.17	6.85	59.01	60.38
Std Dev	14.581	17.155	11.078	16.100	65.897	66.466
Median	1.50	2.00	2.00	1.50	33.00	32.75
Min-Max	0.0-160	0.0-120	0.0-102	0.0-145	0.0-355.0	0.0-337.5
Change from Baseline at Week 24						
N	267	264	273	274	391	186
Mean	0.72	0.31	0.10	0.22	0.62	1.23
Std Dev	2.417	1.903	1.210	1.208	2.692	2.816
Median	0.00	0.00	0.00	0.00	0.00	0.00
Min-Max	-2.5-17.5	-4.5-18.0	-11-9.5	-4.5-9.0	-11.0-19.7	-6.0-12.4
p-value (van Elteren Analysis)		0.0121	0.0014	0.0100	0.0149	

Study MRA229JP

Study MRA229JP was a Phase III, non-inferiority, two-arm, randomized, double blind, active-controlled, parallel group, multi-center study conducted exclusively in Japan in patients with moderate to severe active RA who had an inadequate response to current DMARD therapy including one or more anti-TNF biologic agents. Throughout the study, DMARDs were not permitted, i.e. the patients received TCZ as monotherapy.

This monotherapy study was designed to assess the efficacy and safety of treatment with TCZ 162 mg SC q2w versus TCZ 8 mg/kg IV q4w in Japanese patients with RA. After completion of the double-blind period of 24 weeks, the patients originally assigned to the TCZ IV 8 mg/kg q4w treatment arm received TCZ SC 162 mg in the 84-week open label extension. Patients were to receive TCZ SC q2w, but depending on clinical response the dosing interval could be adjusted to qw or q3w.

Post-hoc analyses were performed on the patients of study MRA229JP to compare the results for All Patients and the subset of patients with RA $\leq$ 2 years at Week 24.

Table 12. ACR20/50/70 response rates in all patients or patients with RA $\leq$ 2 Years at Week 24 - Study MRA229JP (Full Analysis Set)

	All Patients		Early RA Patients (RA≤2 Years)	
	TCZ 162 mg SC qw N=173	TCZ 8 mg/kg IV q4w N=173	TCZ 162 mg SC qw N=51	TCZ 8 mg/kg IV q4w N=32
ACR20, n (%)	137 (79.2)	148 (86.0)	41 (80.4)	27 (87.1)
ACR50, n (%)	108 (62.4)	111 (64.5)	35 (68.6)	23 (74.2)
ACR70, n (%)	63 (36.4)	66 (38.4)	20 (39.2)	11 (35.5)

ACR=American College of Rheumatology; TCZ=tocilizumab; SC=subcutaneous; IV=intravenous; q2w / q4w=once every 2/4 weeks.

Analysis is adjusted for stratification factors body weight category (< 60 kg; ≥60 kg) and previous treatment with TNF antagonist (Yes, No); Last observation carried forward (LOCF) imputation was used for all ACR core set components. CRP used primarily for the calculation of the ACR response, if missing, ESR was substituted.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Studies WA19926 and WA22762 were double blind, active controlled studies in which TCZ was administered every 4 weeks. In Study WA22762, this was given while patients remained on a background non-biologic DMARD (approx. 80% patients received MTX), whilst in Study WA19926 all patients not randomized to monotherapy TCZ, received TCZ in combination with MTX, which was initiated at study start. Both studies used the same outcome measures (e.g. DAS28, ACR response) and utilized the same data collection instruments (e.g. HAQ-DI).

The populations in Study WA22762 and Study WA19926 consisted of patients with moderate to severe active RA. Since Study WA19926 aimed to study TCZ therapy in early RA patients, the RA diagnosis of these patients had to occur within 2 years at the time of the baseline visit. This overlapped in part with the requirement in Study WA22762 that patients could enrol into the trial > 6 months after RA diagnosis.

The efficacy data from the original "All Patient" population of Study WA22762 were compared to those of the subpopulation within the study of patients with early RA (defined by RA diagnosed $\leq$ 2 years of the first TCZ dose) which corresponds to the early RA patients in the WA19926 study. Efficacy data presented focused on the Week 24 analyses when the majority of endpoints from the double-blind periods in both studies were assessed, and before patients in study WA22762 may have been reassigned to a different treatment modality at the Week 24 re-randomization.

Efficacy analysis if further supplemented by radiographic data from the NA25220 study and by the data from TCZ-SC therapy in a monotherapy setting in study MRA229JP.

The efficacy analyses presented in this submission applied the same data handling rules to facilitate comparison across studies.

Efficacy data and additional analyses

The patients in the RA < 2 years and All Patients populations of WA22762 and patients in WA19926 had similar baseline characteristics with a few exceptions.

As expected, the main difference was the duration of disease, where the median was 5.8 and 6.2 years for the All Patients groups of WA22762, and ranged from 0.3 to 1.1 years in WA19926 and in the WA22762 patient groups with RA $\leq$ 2 years. The patients with early RA in WA22762 and WA19926 were 3 to 4 years younger than in the overall WA22762 population, which is consistent with their shorter disease duration.

Disease activity was similar across the 3 populations (WA19926, WA22762 All Patients and RA < 2 years).

Efficacy was demonstrated at Week 24 in all the patient groups for both the IV and SC routes of administration, across the following key efficacy endpoints: ACR 20/50/70, DAS28 < 2.6 (remission), DAS28 < 3.2 (low disease activity) and HAQ-DI decrease $\geq$ 0.3.

In study WA22762, the data from patients with early RA demonstrated robust efficacy attainment with the SC formulation that was consistent with that seen in the All Patient population: ACR20 response rate of 68.2% vs 67.7% and a DAS28 remission response rate of 35.6% vs 34.4%.

The observed efficacy (ACR 20/50/70, DAS28 < 2.6 (remission), DAS28 < 3.2 (low disease activity) and HAQ-DI decrease $\geq$ 0.3 at Week 24) was maintained over the entire 2-year duration of either study.

Although some parameters showed fluctuation in the response rates across different points in time, the RA ≤ 2 years subpopulation was generally showed response rates that were consistent with those in the corresponding All Patients groups in Study WA22762.

In study WA22762 numerically higher ACR responses were observed in early RA patients treated with TCZ IV 8mg/kg q4w weeks than in patients treated with TCZ SC 162 mg qw at Week 24. However this was not reflected in the DAS28 outcomes which unlike ACR responses are based on absolute values rather than changes from baseline. The observed differences in the changes of relative but not in absolute values of efficacy between the two administration modes therefore are likely to be the reflection of the different patient characteristics of the analyzed subpopulations, as these were not subject to the randomization but defined post-hoc. Furthermore, these differences in the ACR responses were not observed consistently at all time-points prior to week 24.

A difference was also observed between treatment arms for HAQ-DI for the early RA population. The difference was most notable at the Week 24 visit. However, the change from baseline scores at this time point for each treatment arm demonstrated similar distributions. In addition it was noted that that the lower quartile in the SC arm fell just above the selected cut-off value for HAQ-DI while that of the IV arm was just under. Even though this difference has no clinical relevance, it is likely to overestimate any differences between the treatment arms when HAQ-DI is analyzed as a binary endpoint.

In the long term efficacy analysis at Year 2, the RA ≤ 2 years TCZ-SC group exhibited numerically higher responses than TCZ-IV for all the efficacy parameters except HAQ-DI responses. The latter observation again could be explained by the categorical distribution of the responses, but overall there is no suggestion that the SC and IV administration in early RA patients would have differential efficacy after 2 years of treatment with TCZ.

Reductions in the progression of joint damage were observed in both studies, Study WA19926 and Study NA2522. The van der Heijde modified Total Sharp Score (mTSS) showed robust reductions in the TCZ 8 mg/kg IV or TCZ 162 mg SC q2w groups versus the corresponding placebo groups.

2.4.3. Conclusions on the clinical efficacy

Sufficient evidence has been provided to demonstrate that the efficacy of the SC TCCZ formulation would be similar between patients with a diagnosis of RA ≤ 2 years and the overall RA population irrespective of time from diagnosis. The totality of the data, also demonstrated that the SC formulation of TCZ would be equally efficacious with the IV TCZ formulation in patients with a diagnosis of RA ≤2 years.

2.5. Clinical safety

Introduction

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.

In both pivotal studies Study WA22762 and Study WA19926 as well as in the supportive studies NA25220 and MRA229JO, no new safety signals were identified during the original assessment.

The primary safety comparison within this submission was between the safety data from studies WA22762

(All Patients and subpopulation with disease duration ≤ 2years) and WA19926.

Patient exposure

In the All patients population the total cumulative duration in Study WA22762 for the SC and the IV formulations were 1013.26 and 816.53 patient years (PY) respectively. For patients with disease duration ≤ 2 years, total cumulative duration was 210.29 and 160.60 PY in the SC and IV arms, respectively. For the patients in the 8 mg/kg + MTX arm from study Study WA19926, this was 487.94 PY.

In Study WA22762, if a patient was assigned to a different route of TCZ administration at the re-randomization at Week 24, then duration was derived up to the point of switching. To allow better comparison across treatment groups, data from patients who were re-randomized to a different route of administration at Week 24 (Study WA22762) are included only up to the point of changing treatment regimen, and the data are presented as rates per 100 patient years (PY) to account for differences in exposure.

The data for WA19926 include only those from patients who were assigned to TCZ 8 mg/kg IV qw + MTX at the beginning of the study but not of those who received this dose as escape therapy as consequence of an insufficient therapeutic response to an another dose.

Baseline demographic and disease characteristics in the safety population are summarised in **Table 13**.

Table 13. Baseline demographic and disease characteristics (Studies WA22762 and WA19926: Safety population)

	WA22762				WA19926
	All Patients		Patients with RA≤2 Years		
	TCZ 162 mg SC qw+DMARD n=631	TCZ 8 mg/kg IV q4w+DMARD n=631	TCZ 162 mg SC qw+DMARD n=131	TCZ 8 mg/kg IV q4w+DMARD n=127	TCZ 8 mg/kg IV q4w+MTX n=290
Baseline Demographic Characteristics					
Female, n (%)	520 (82%)	521 (83%)	103 (79%)	98 (77%)	228 (79%)
Caucasian, n (%)	486 (77%)	479 (76%)	98 (75%)	92 (72%)	229 (79%)
Age, years					
Mean (± SD)	53 (12.4)	53 (12.5)	50.4 (14.0)	49.1 (14.4)	49.5 (13.7)
Range	18 – 83	18 – 86	18 – 83	21 – 86	18 – 79
Body weight, kg					
Mean (± SD)	75 (19.1)	74 (19.0)	77 (21.6)	77 (19.2)	74.8 (19.3)
Range	38 – 150	32 – 150	40 – 150	42 – 141	42 – 150
Baseline Disease Characteristics: Mean (±SD)					
RA duration, years					
Mean (± SD)	8.7 (8.3)	8.6 (8.1)	1.2 (0.4)	1.1 (0.4)	0.5 (0.5)
Median	5.8	6.2	1.1	1.0	0.3
DAS28	6.6 (1.0)	6.7 (1.0)	6.6 (1.1)	6.8 (1.0)	6.7 (1.1)
HAQ-DI	1.6 (0.6)	1.7 (0.6)	1.5 (0.7)	1.6 (0.7)	1.5 (0.6)
No. of previous DMARDs	1.4 (0.7)	1.4 (0.7)	1.4 (0.6)	1.5 (0.6)	0.2 (0.5)
Oral corticosteroids, n (%)	344 (55%)	338 (54%)	73 (55%)	66 (52%)	95 (33%)
TNF-IR, n (%)	142 (22%)	136 (22%)	11 (8%)	10 (8%)	0 (0%)

Adverse events

Table 14. Rates of adverse events by the most frequently reported body systems (Year 2, safety population)

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ 162 mg SC qw + DMARD N = 631	TCZ 8 mg/kg IV q4w + DMARD N = 631	TCZ 162 mg SC qw + DMARD N = 131	TCZ 8 mg/kg IV q4w + DMARD N = 127	TCZ 8 mg/kg IV q4w + MTX N = 290
Exposure (PY)	1013.26	816.53	210.29	160.60	487.94
Infections and Infestations					
Patients with at least one AE (Number of Events)	399 (1101)	365 (862)	82 (207)	68 (132)	169 (440)
Rate per 100 PY	108.66	105.57	98.44	82.19	90.18
Investigations					
Patients with at least one AE (Number of Events)	238 (527)	178 (378)	62 (122)	52 (107)	150 (268)
Rate per 100 PY	52.01	46.29	58.02	66.63	54.92
Gastrointestinal Disorders					
Patients with at least one AE (Number of Events)	212 (366)	179 (317)	49 (67)	40 (75)	134 (283)
Rate per 100 PY	36.12	38.82	31.86	46.70	58.00
Musculoskeletal and Connective Tissue Disorders					
Patients with at least one AE (Number of Events)	205 (330)	174 (312)	31 (54)	32 (53)	78 (142)
Rate per 100 PY	32.57	38.21	25.68	33.00	29.10
General Disorders and Administration Site Conditions					
Patients with at least one AE (Number of Events)	131 (389)	76 (175)	25 (53)	16 (20)	33 (34)
Rate per 100 PY	38.39	21.43	25.20	12.45	6.97
Skin and Subcutaneous Tissue Disorders					
Patients with at least one AE (Number of Events)	130 (185)	118 (181)	22 (26)	24 (38)	58 (80)
Rate per 100 PY	18.26	22.17	12.36	23.66	16.40

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ 162 mg SC qw + DMARD N = 631	TCZ 8 mg/kg IV q4w + DMARD N = 631	TCZ 162 mg SC qw + DMARD N = 131	TCZ 8 mg/kg IV q4w + DMARD N = 127	TCZ 8 mg/kg IV q4w + MTX N = 290
Injury, Poisoning and Procedural Complications					
Patients with at least one AE (Number of Events)	119 (243)	89 (142)	14 (25)	14 (23)	44 (66)
Rate per 100 PY	23.98	17.39	11.89	14.32	13.53
Nervous System Disorders					
Patients with at least one AE (Number of Events)	118 (179)	104 (160)	23 (32)	22 (29)	49 (73)
Rate per 100 PY	17.67	19.60	15.22	18.06	14.96
Blood and Lymphatic System Disorders					
Patients with at least one AE (Number of Events)	97 (163)	97 (155)	22 (53)	25 (34)	26 (40)
Rate per 100 PY	16.09	18.98	25.20	21.17	8.20
Respiratory, Thoracic and Mediastinal Disorders					
Patients with at least one AE (Number of Events)	102 (143)	91 (134)	19 (24)	19 (24)	55 (79)
Rate per 100 PY	14.11	16.41	11.41	14.94	16.19
Metabolism and Nutrition Disorders					
Patients with at least one AE (Number of Events)	101 (123)	86 (103)	20 (26)	17 (20)	27 (36)
Rate per 100 PY	12.14	12.61	12.36	12.45	7.38
Vascular Disorders					
Patients with at least one AE (Number of Events)	80 (92)	86 (112)	16 (20)	17 (22)	39 (43)
Rate per 100 PY	9.08	13.72	9.51	13.70	8.81

An elevated GI AE rate in the Early RA subpopulation of IV TCZ arm of WA22762 study was observed but this was mostly driven by the multiple occurrences of AEs in a number of individual patients (data not shown).

Serious adverse event / deaths / other significant events

Table 15. Overview of serious adverse events per 100 Patient Years (Year 2, safety population)

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ 162 mg SC qw + DMARD N = 631	TCZ 8 mg/kg IV q4w + DMARD N = 631	TCZ 162 mg SC qw + DMARD N = 131	TCZ 8 mg/kg IV q4w + DMARD N = 127	TCZ 8 mg/kg IV q4w + MTX N = 290
Exposure (PY)	1013.26	816.53	210.29	160.60	487.94
Infections and Infestations					
Patients with at least one AE (Number of Events)	31 (40)	27 (32)	5 (5)	4 (4)	15 (17)
Rate per 100 PY	3.95	3.92	2.38	2.49	3.48
Nervous System Disorders					
Patients with at least one AE (Number of Events)	11 (14)	14 (15)	0	4 (5)	5 (6)
Rate per 100 PY	1.38	1.84		3.11	1.23
Musculoskeletal and Connective Tissue Disorders					
Patients with at least one AE (Number of Events)	10 (10)	16 (17)	1 (1)	1 (1)	4 (4)
Rate per 100 PY	0.99	2.08	0.48	0.62	0.82
Injury, Poisoning and Procedural Complications					
Patients with at least one AE (Number of Events)	10 (15)	10 (10)	0	0	5 (5)
Rate per 100 PY	1.48	1.22			1.02
Cardiac Disorders					
Patients with at least one AE (Number of Events)	9 (12)	4 (4)	3 (3)	2 (2)	5 (6)
Rate per 100 PY	1.18	0.49	1.43	1.25	1.23
Gastrointestinal Disorders					
Patients with at least one AE (Number of Events)	9 (12)	7 (8)	1 (1)	1 (1)	4 (4)
Rate per 100 PY	1.18	0.98	0.48	0.62	0.82
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)					
Patients with at least one AE (Number of Events)	11 (11)	6 (7)	0	2 (2)	3 (3)
Rate per 100 PY	1.09	0.86		1.25	0.61
Respiratory, Thoracic and Mediastinal Disorders					
Patients with at least one AE (Number of Events)	4 (5)	7 (9)	1 (2)	1 (1)	4 (4)
Rate per 100 PY	0.49	1.10	0.95	0.62	0.82

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

Sorting of SOCs by overall frequency of all events per body system across all presented treatment groups.

Table 16. Overview of death per 100 Patient Years (Year 2, safety population)

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ 162 mg SC qw + DMARD N = 631	TCZ 8 mg/kg IV q4w + DMARD N = 631	TCZ 162 mg SC qw + DMARD N = 131	TCZ 8 mg/kg IV q4w + DMARD N = 127	TCZ 8 mg/kg IV q4w + MTX N = 290
Exposure (PY)	1013.26	816.53	210.29	160.60	487.94
Deaths	4	4	0	1	4
Rate per 100 PY	0.39	0.49	0.00	0.62	0.82
95% CI	[0.11, 1.01]	[0.13, 1.25]	[0.00, 1.75]	[0.02, 3.47]	[0.22, 2.10]

The causes of death in Study WA22762 were shock, thrombosis, death (not otherwise specified), cerebral infarction, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, sepsis, ischaemic cerebral infarction) and ins Study WA19926 (interstitial lung disease, pneumothorax, endometrial cancer, hypoglycaemic coma).

Four of these events (shock, death, acute respiratory distress syndrome and sepsis) were assessed as "related" to TCZ treatment by the investigators.

The only death reported in the Early RA subgroup (idiopathic pulmonary fibrosis) was considered "unrelated to TCZ treatment by the investigator.

Adverse events of special interest

The types of AEs were predefined based on findings from nonclinical and clinical studies with TCZ, safety concerns for the RA population (e.g., cardiovascular risk, malignancies), as well as the safety profile of other monoclonal antibodies used in RA.

Infections

Table 17. Overview of infection adverse events per 100 Patient Years (Year 2, safety population)

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ 162 mg SC qw + DMARD N = 631	TCZ 8 mg/kg IV q4w + DMARD N = 631	TCZ 162 mg SC qw + DMARD N = 131	TCZ 8 mg/kg IV q4w + DMARD N = 127	TCZ 8 mg/kg IV q4w + MTX N = 290
Exposure (PY)	1013.26	816.53	210.29	160.60	487.94
Patients with Infections (Number of Events)	399 (1101)	365 (862)	82 (207)	68 (132)	169 (440)
Rate per 100 PY	108.66	105.57	98.44	82.19	90.18
95% CI	[102.34, 115.27]	[98.64, 112.86]	[85.48, 112.80]	[68.77, 97.47]	[81.95, 99.01]
Patients with Serious Infections (Number of Events)	31 (40)	27 (32)	5 (5)	4 (4)	15 (17)
Rate per 100 PY	3.95	3.92	2.38	2.49	3.48
95% CI	[2.82, 5.38]	[2.68, 5.53]	[0.77, 5.55]	[0.68, 6.38]	[2.03, 5.58]
Deaths from Infections	0	1	0	0	0
Rate per 100 PY	0.00	0.12	0.00	0.00	0.00
95% CI	[0.00, 0.36]	[0.00, 0.68]	[0.00, 1.75]	[0.00, 2.30]	[0.00, 0.76]
Patients with Serious Opportunistic Infections (Number of Events)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Rate per 100 PY	[0.30]	0.00	0.00	0.00	0.00
95% CI	[0.06, 0.87]	[0.00, 0.45]	[0.00, 1.75]	[0.00, 2.30]	[0.00, 0.76]

Multiple occurrences of the same adverse event in one individual are counted.
Output only contains preferred terms with a Primary System Organ Class of Infections and Infestations.

The most frequent types of all infections across all treatment groups were upper respiratory tract infection, followed by nasopharyngitis and urinary tract infection. The distribution of the various types of infections was overall similar among all groups.

The most common serious infections occurring in Study WA22762 were cellulitis (8 patients SC versus 1 patient IV, respectively) and pneumonia (4 patients versus 6 patients). Cellulitis and pneumonia (5 events each) were also the most common serious infections in the TCZ 8 mg/kg IV arm of Study WA19926. Urinary tract infection was the only type of serious infection that was seen more than once in the same treatment group of the RA $\leq$ 2 years WA22762 subpopulation. Serious infections were not associated with Grade 3 or 4 neutropenia.

Hypersensitivity reactions

Table 18. Overview of hypersensitivity and anaphylaxis adverse events per 100 Patient Years (Year 2, safety population)

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ 162 mg SC qw + DMARD N = 631	TCZ 8 mg/kg IV q4w + DMARD N = 631	TCZ 162 mg SC qw + DMARD N = 131	TCZ 8 mg/kg IV q4w + DMARD N = 127	TCZ 8 mg/kg IV q4w + MTX N = 290
Exposure (PY)	1013.26	816.53	210.29	160.60	487.94
Patients with Hypersensitivity Reactions (Number of Events)	58 (89)	75 (121)	11 (12)	14 (20)	64 (90)
Rate per 100 PY	8.78	14.82	5.71	12.45	18.45
95% CI	[7.05, 10.81]	[12.30, 17.71]	[2.95, 9.97]	[7.61, 19.23]	[14.83, 22.67]
Patients with Clinically Significant Hypersensitivity Reactions (Number of Events)	10 (12)	12 (12)	2 (2)	5 (5)	9 (9)
Rate per 100 PY	1.18	1.47	0.95	3.11	1.8
95% CI	[0.61, 2.07]	[0.76, 2.57]	[0.12, 3.44]	[1.01, 7.27]	[0.8, 3.5]
Patients with Serious Hypersensitivity Reactions (Number of Events)	5 (5)	2 (2)	0 (0)	0 (0)	1 (1)
Rate per 100 PY	0.49	0.24	0.00	0.00	0.20
95% CI	[0.16, 1.15]	[0.03, 0.88]	[0.00, 1.75]	[0.00, 2.30]	[0.01, 1.14]
Patients with Anaphylaxis (Number of Events)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rate per 100 PY	0.00	0.00	0.00	0.00	0.00
95% CI	[0.00, 0.36]	[0.00, 0.45]	[0.00, 1.75]	[0.00, 2.30]	[0.00, 0.76]

There were no events of anaphylaxis that met Sampson's Criteria in any of the 5 patient groups investigated in this comparison. The early RA patients in Study WA22762 had no serious hypersensitivity reactions and the 1 serious event (transaminases increased) recorded in the early RA patients in Study WA19926 (TCZ 8 mg/kg + MTX) was not clinically consistent with hypersensitivity.

Malignancies

In All Patients from WA22762, similar rates of malignancies (either serious or non-serious events) were observed between the TCZ-IV and TCZ-SC treatment groups. In the early RA patients (treated with TCZ-IV), there was 1 malignancy SAE (invasive ductal breast carcinoma).

Serious myocardial infarction, serious stroke adverse events

There were no serious myocardial infarctions in any early RA patients in Study WA22762, consistent with the rates observed in All Patients in Study WA22762 and the TCZ 8 mg/kg IV group in Study WA19926.

There were 0 (TCZ-SC) and 2 (TCZ-IV) serious stroke events in the Study WA22762 early RA patients, consistent with the rates observed in All Patients in Study WA22762 and the TCZ 8 mg/kg IV group in Study WA19926.

Serious bleeding event

In Study WA22762, 12 patients reported serious bleeding events in the All Patients group, with 5 in the SC arm (anastomotic ulcer haemorrhage, gastric ulcer haemorrhage, hepatic haematoma, haematoma, cerebral haemorrhage) and 7 in the IV arm (rectal haemorrhage, haematuria, haemorrhagic stroke, haemorrhoidal haemorrhage, haemorrhagic intestinal diverticulum, haematoma, and post procedural haemorrhage). In the 8 mg/kg + MTX group of Study WA19926, 3 patients experienced serious bleeding (gastrointestinal haemorrhage, contusion, and haematuria).

There were no serious bleeding events in the TCZ-SC WA22762 early RA patients.

None of the serious bleeding AEs in either study were associated with a platelet count below the normal range. There was no association between thrombocytopenia (> Grade 3) and serious bleeding events identified in either study.

Gastrointestinal perforations

There was a single event (diverticular perforation) of medically confirmed serious gastrointestinal perforation in the SC arm of the WA22762 All Patients group. There were no events in the other patient groups.

Serious hepatic events

Two patients in the IV arm of Study WA22762 (All Patients) had a total of 3 serious hepatic events (hepatic steatosis, hepatic encephalopathy [2 events in the same patient]). The patient with 2 events of hepatic encephalopathy was also in the subgroup of patients with RA $\leq$ 2 years. There were no additional serious hepatic events in other patient groups in both studies

No patients met the criteria for Hy's law in either study.

Demyelinating disorders

Demyelinating events were assessed because they have previously been observed in association with TCZ IV treatment and with TNF-inhibitor treatment in RA patients.

No demyelinating disorders were reported in either study.

Laboratory findings

- **ALT, AST and Bilirubin**

The changes in the liver profile observed in Study WA22762 showed a similar pattern between TCZ-SC and TCZ-IV in both All Patients and the early RA subpopulation.

In Study WA19926 (MTX-naïve patients who received TCZ IV + MTX), there was a higher incidence of patients with an increased ALT level who experienced an NCI CTCAE Grade 2 or 3 elevation compared to that in DMARD experienced patients in Study WA22762; no other notable differences were observed.

There were no reported clinical manifestations of hepatic injury associated with elevations in AST, ALT, or total bilirubin levels in either study. No patient met the criteria for Hy's law in WA22762 or WA19926.

- **Neutrophils, platelets**

Table 19. Worst CTC grades for neutropenia and thrombocytopenia (Year 2) in WA22762 (ITT Population continuing Beyond Week 24) and WA19926 Studies (safety population)

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ 162 mg SC qw + DMARD N = 521	TCZ 8 mg/kg IV q4w + DMARD N = 372	TCZ 162 mg SC qw + DMARD N = 107	TCZ 8 mg/kg IV q4w + DMARD N = 75	TCZ 8 mg/kg IV q4w + MTX N=290
Neutrophils					
Normal	288 (55.3%)	229 (61.6%)	57 (53.3%)	43 (57.3%)	167 (57.6%)
Grade 1	113 (21.7%)	74 (19.9%)	23 (21.5%)	18 (24.0%)	55 (19.0%)
Grade 2	89 (17.1%)	44 (11.8%)	20 (18.7%)	11 (14.7%)	54 (18.6%)
Grade 3	28 (5.4%)	25 (6.7%)	6 (5.6%)	3 (4.0%)	14 (4.8%)
Grade 4	3 (0.6%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Platelets					
Normal	451 (86.6%)	307 (82.5%)	94 (87.9%)	62 (82.7%)	256 (88.3%)
Grade 1	67 (12.9%)	62 (16.7%)	12 (11.2%)	12 (16.0%)	32 (11.0%)
Grade 2	3 (0.6%)	2 (0.5%)	1 (0.9%)	1 (1.3%)	1 (0.3%)
Grade 3	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

- **Lipids**

The lipid profile consisted of fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Overall, the changes in the lipid profile observed in the SC TCZ arm were comparable with the changes observed in the IV TCZ arm in the All Patients and $\leq$ 2 years populations of Study WA22762. There was no trend for any difference between the two arms for shifts from baseline value to last observation when total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were compared in the SC or IV TCZ arms of both the All Patients and the RA $\leq$ 2 year populations.

The lipid profile in study WA19926 was generally similar to that seen in Study WA22762.

- **Vital signs**

No clinically relevant differences over time were observed in vital sign parameters (i.e., diastolic and systolic blood pressure) for patients in the two studies.

- **Immunogenicity**

The proportion of patients developing anti-TCZ antibodies that were confirmation assay positive post-baseline was < 2% in any treatment group. None of the patients in the all 5 treatment groups had an anaphylaxis event (as defined by Sampson's criteria). Among the patients who developed anti-TCZ antibodies, none experienced a serious hypersensitivity reaction.

No sub-analysis of WA22762 patients with RA $\leq$ 2 years was carried out as the number of patients with anti-TCZ antibodies was so low that the data would be difficult to interpret.

Safety in special populations

Given the relatively small number of patients in the WA22762 RA $\leq$ 2 years subpopulation, no analyses based on demographic and other intrinsic factors (age, gender, race, weight, BMI, medical history) were performed for the safety data presented here for the purpose of bridging between the data obtained with the

SC formulation and the IV results in a population with early RA.

No analyses based on environmental and other extrinsic factors (previous treatment with ant-TNFs, corticosteroids, DMARDs, region, smoking status) were performed for the safety data presented here for the purpose of bridging between the data obtained with the SC formulation and the IV results in a population with early RA.

Pregnancy

In the study WA22762, 4 (SC arm) and 5 (IV arm) patients reported a pregnancy. Two of these patients were in the RA≤2 years subpopulation (both SC). The outcome of these two pregnancies were were spontaneous abortion and vaginal birth (with normal outcome for the infant).

The outcomes of the remaining cases of pregnancy were three C-section births (with normal outcomes for the infants in two cases and one unknown), two spontaneous abortions, 1 therapeutic abortion, and 1 case was lost to follow up.

In study WA19926, 4 patients in the TCZ 8 mg/kg+MTX group became pregnant. The outcomes of these pregnancies were: 1 vaginal birth (with normal outcome for the infant), 2 spontaneous abortions, and 1 patient was lost to follow up.

Discontinuation due to adverse events

Table 20. Overview of adverse events leading to withdrawal per 100 Patient Years (Year 2, safety population)

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ 162 mg SC qw+DMARD N=631	TCZ 8 mg/kg IV q4w+DMARD N=631	TCZ 162 mg SC qw+DMARD N=131	TCZ 8 mg/kg IV q4w+DMARD N=127	TCZ 8 mg/kg IV q4w+MTX N=290
Exposure (PY)	1013.26	816.53	210.29	160.60	487.94
Patients Withdrawn for AE (Number of Events)	68 (91)	66 (80)	13 (13)	19 (23)	66 (66)
Rate per 100 PY	8.98	9.80	6.18	14.32	13.53
95% CI	[7.23, 11.03]	[7.77, 12.19]	[3.29, 10.57]	[9.08, 21.49]	[10.46, 17.21]

The distribution of AEs leading to withdrawal across SOCs was in general consistent among the presented treatment groups. Overall, among all 5 treatment groups, the 2 most frequently affected SOCs were Investigations (driven primarily by withdrawals due to AEs of elevations of liver enzymes) and Infections and Infestations.

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The rate of all AEs for TCZ-SC in the early RA subpopulation is consistent with that from the All Patient population. The SAE rate in early RA patients was numerically higher (the data interpretation is limited due to the small PY exposure).

There were no deaths in the TCZ-SC arm in the study.

The distribution of AEs and SAEs across SOCs was not different from the overall TCZ safety profile.

Post marketing experience

Regular pharmacovigilance activities of post-marketing data have not revealed new information that would change the safety profile of TCZ of the IV or SC routes of administration to RA patients as established in clinical trials.

2.5.1. Discussion on clinical safety

Data from the pivotal Phase III study used to support approval of the SC formulation (Study WA22762) were compared with data from study WA19926 (8 mg/kg IV dose arm) used to support early RA treatment, in order to compare the safety data on the use of the SC dosage form of TCZ with the safety data obtained during the study of patients with early RA. The safety data of both studies have been assessed previously.

The main difference between the Study WA22762 and Study WA19926 populations was that the former had to have an inadequate clinical response to at least one DMARD, which may have included anti-TNFs (up to 20%). On the other hand, the early RA population of study WA19926 included only MTX-naïve patients with baseline RA duration of < 2 years. To ensure that this was also a population with active and progressive RA disease the selection criteria enriched for patients with high disease activity score, serologic positivity and/or joint erosions.

The analysis focus on the results obtained from 5 treatment groups, including the TCZ-SC and TCZ-IV groups in the subset of early RA patients (RA diagnosis within < 2 years of their first dose) in Study WA22762, the All Patients TCZ-SC and TCZ-IV groups in WA22762, and the TCZ 8 mg/kg IV q4w + MTX arm of Study WA19926. For Study WA22762, information presented for patients who were re-randomized to a different route of administration at Week 24 have their data included only up to the point of switch in treatment.

The rates of SAEs per 100 PY were consistent across all treatment groups in Study WA22762 and Study WA19926 (range: 12.09 to 15.43). A numerically lower rate was observed in early RA patients treated with TCZ-SC in WA22762 (7.61 per 100 PY [95% CI: 4.35, 12.36]). However with regard to “blood and lymphatic system disorder” a numerical higher rate was observed in the early RA patients in Study WA22762. The MAH should detail these events.

Although the distribution of affected SOCs was well balanced, some differences in AE rates were observed. There was an imbalance in WA22762 in the AE rates in the General Disorders and Administration Site Conditions SOC, with higher rates observed in TCZ-SC than in TCZ-IV treated patients and also higher in WA22762 overall than in WA19926. These differences are not unexpected due to the higher rate of injection site reactions following SC treatment.

In WA19926 TCZ 8 mg/kg IV treatment+ MTX arm GI disorders was experienced with much higher AE rate, primarily driven by nausea. This was consistent with the known gastrointestinal problems most commonly reported with MTX, as patients enrolled in WA19926 were MTX-naive patient at baseline.

The number of deaths was small, with the rates of death broadly comparable across the different patient groups, with the 95% CIs broadly overlapping. The death rates were thus ranging between 0.00 deaths per 100 PY (95% CI: 0.00, 1.75) and 0.82 deaths per 100 PY (95% CI: 0.22, 2.10).

No new signals emerged from the analysis of the adverse events of special interest predefined on the basis of findings from previous clinical studies and known safety concerns for the RA population.

The rate of serious infections in Study WA22762 was balanced between the TCZ-SC and TCZ-IV groups and was numerically lower in RA < 2 years patients than in All Patients.

The rate of infections in the WA22762 early RA subpopulation was numerically higher in TCZ-SC than in TCZ-IV patients, but was within the range of those in the WA22762 All Patients and the WA19926 TCZ IV 8 mg/kg + MTX groups. The distribution of the various types of infections was overall similar among all groups

The early RA patients in Study WA22762 had no serious hypersensitivity reactions. There were no events of anaphylaxis that met Sampson’s Criteria in any of the 5 patient groups investigated in this comparison.

In the early RA patients in Study WA22762 there was a single event of serious malignancy (invasive ductal breast carcinoma) in the TCZ-IV group.

There were no serious myocardial infarctions, stroke, serious bleeding, and gastrointestinal perforations in any early RA patients in Study WA22762, consistent with the low rates observed in All Patients in Study WA22762 and the TCZ 8 mg/kg IV group in Study WA19926.

Two patients in the IV arm of Study WA22762 (All Patients) had a total of 3 serious hepatic events. The patient with 2 events of hepatic encephalopathy was also in the subgroup of patients with RA < 2 years.

No events of demyelinating disorders were reported in either study.

The rate per 100 PY of AEs leading to withdrawal in the TCZ-SC patients in the WA22762 early RA subpopulation was numerically lower than in the TCZ IV early RA patients in either study.

The changes in the liver profile i.e. AST, ALT, or total bilirubin levels observed in study WA22762 were similar when comparing the SC and IV arms in the All Patient and the RA < 2 year populations. There were no reported clinical manifestations of hepatic injury associated with elevations in AST, ALT, or total bilirubin levels. No patient met the laboratory criteria for Hy's law.

No patients in the relevant patient groups who had a Grade 3/4 neutropenia had a serious infection. None of the patients who reported a serious infection had a low neutrophil count within 30 days of the infection.

Thrombocytopenia was a rare occurrence in Study WA22762. Two events were observed in patients with RA < 2 years.

Differences between treatment arms with regards to the lipid profile in were minor and are not considered to be clinically relevant.

No clinically relevant differences over time were observed in vital sign parameters (i.e., diastolic and systolic blood pressure) for patients in the two studies.

The proportion of patients developing anti-TCZ antibodies that were confirmation assay positive post-baseline was < 2% in any treatment group.

2.5.2. Conclusions on clinical safety

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

The safety profiles observed in early RA patients treated in Study WA22762 with TCZ-SC or TCZ-IV is consistent with the safety profile observed in the All Patients Population in this study and within the range of the safety profile observed in Study WA19926 (IV TCZ 8 mg/kg + MTX). These results demonstrate that there are no clinically relevant differences in the safety profile of TCZ in early RA in comparison with All Patient population considering the SC administration routes. Differences/trends of differences in AE rates were related to the different routes of adminsitaritn rather than the different RA subpopulations. Possible clinical significance (if any) of these trends can be revealed via long-term follow-up using data (SC and IV) from the ongoing registries which are described in the risk management plan.

All safety concerns are adequately managed through warnings in the SmPC and appropriate risk minimisation measures in the risk management plan.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 10 October 2016.

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 plan version 18.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 18.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Serious infection Complications of diverticulitis Serious hypersensitivity reactions Neutropenia
Important potential risks	Neutropenia and the potential risk of infections Thrombocytopenia and the potential risk of bleeding Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity Elevated lipid levels and the potential risk of cardiovascular and 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

Summary of safety concerns in Paediatric Patients	
Important identified risks	Serious Infection Serious hypersensitivity reactions Neutropenia
Important potential risks	Skeletal development Immunogenicity Malignancies CYP450 enzyme normalization
Missing information	MAS in sJIA patients

Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
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		Ongoing	Clinical Study Report Expected 2017
Paediatric Registry (WA29358): Observational Safety and Effectiveness Study of Patients with Polyarticular	To assess the long-term safety and effectiveness of TCZ in relation to comparator biologics in the treatment of pJIA in a real-world setting for 5	Safety in pediatric patients	Protocol agreed 22 January 2015.	Implementation date to be confirmed Q3 2014. Final CSR date expected August

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Juvenile Idiopathic Arthritis Treated with Tocilizumab	years.			2029.
WA28029	To evaluate decreased dose frequency in patients with sJIA who experience laboratory abnormalities during treatment with TCZ	Safety in pediatric patients	Ongoing	First patient first visit June 2013 Final CSR Q4 2016
NP25737	A pharmacokinetic and safety study of TCZ in patients less than 2 years old with active sJIA	Safety profile in pediatric patients less than 2 years old	Ongoing	Final CSR expected November 2017
WA25204 (ENTRACTE)	A clinical outcomes study to evaluate the effects of IL-6 receptor blockade with tocilizumab (TCZ) in comparison with etanercept (ETA) on the rate of cardiovascular events in patients with moderate to severe rheumatoid arthritis (RA).	Cardiovascular events	Ongoing	Final CSR expected Q1 2017

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Serious Infections	SmPC PIL	Patient Alert Card; Patient Brochure; Healthcare Provider Brochure
Complications of diverticulitis	SmPC PIL	Patient Alert Card; Patient Brochure; Healthcare Provider Brochure
Serious Hypersensitivity Reactions	SmPC PIL	Patient Alert Card; Patient Brochure;

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		Healthcare Provider Brochure; Rheumatoid Arthritis Dosing Guide
Neutropenia	SmPC PIL	Patient Brochure; Healthcare Provider Brochure
Important Potential Risks		
Neutropenia and the potential risk of infection	SmPC PIL	Patient Brochure; Healthcare Provider Brochure
Thrombocytopenia and the potential risk of bleeding	SmPC	Patient Brochure; Healthcare Provider Brochure
Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity	SmPC PIL	Patient Brochure; Healthcare Provider Brochure
Elevated Lipid Levels and Potential Risk of Cardiovascular/ Cerebrovascular Events	SmPC PIL	Patient Brochure; Healthcare Provider Brochure
Malignancies	SmPC	Patient Brochure; Healthcare Provider Brochure
Demyelinating disorders	SmPC	Healthcare Provider Brochure
Immunogenicity	SmPC	None proposed
Skeletal development (in paediatric patients)	None proposed	Not applicable
Missing Information		
CYP450 enzyme normalisation	SmPC PIL	None proposed
Macrophage Activation Syndrome in sJIA Patients	SmPC PIL	Patient Alert Card
Paediatric patients	SmPC PIL	None proposed
Elderly Patients	SmPC	None proposed
Effects during pregnancy	SmPC PIL	None proposed
Hepatic impairment	SmPC PIL	None proposed
Renal Impairment	SmPC PIL	None proposed
Combination with biologics	SmPC PIL	None proposed
Safety in patients <60 kg in switcher population	SmPC (SC Use)	None proposed
Long-term safety in the switcher patient population	SmPC (SC Use)	None proposed
IgE Data Following TCZ SC Treatment	SmPC	None proposed
Source: Table V.3 Summary table of RMM, EU RMP v18.1 (PDF version), p292–344. SmPC: Summary of Product Characteristics PIL: Patient Information Leaflet		

2.7. Update of the Product information

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

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

Changes to the leaflet from the proposed new indication have been user tested during the procedure number EMEA/H/C/N0053 and approved by the CHMP on July 2, 2015.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Efficacy was demonstrated in studies WA22762 and WA19926 at Week 24 in all the patient groups, including the early RA subpopulation for both the IV and SC routes of administration, across the following key efficacy endpoints: ACR 20/50/70, DAS28 < 2.6 (remission), DAS28 < 3.2 (low disease activity) and HAQ-DI decrease > 0.3. In study WA22762, the data from patients with early RA demonstrated robust efficacy that was consistent with that seen in the All Patient population: ACR20 response rate of 68.2% vs 67.7% and a DAS28 remission response rate of 35.6% vs 34.4%.

The observed efficacy (ACR 20/50/70, DAS28 < 2.6 (remission), DAS28 < 3.2 (low disease activity) and HAQ-DI decrease > 0.3 at Week 24 was maintained over the entire 2-year duration of both studies.

Reductions in the progression of joint damage were observed in both studies, Study WA19926 and Study NA25220. The van der Heijde modified Total Sharp Score (mTSS) showed reductions in the TCZ 8 mg/kg IV or TCZ 162 mg SC q2w groups versus the corresponding placebo groups.

Uncertainty in the knowledge about the beneficial effects

The efficacy evaluation was based on an unplanned analysis of subpopulations. As a consequence the numbers of patients contributing to efficacy data varied between treatment groups and studies.

Comparison of the results between studies is to some extent limited by the fact there were differences between patient populations in these studies regarding previous exposure to biologic and non-biologic DMARDS. However, the overall experience with TCZ in early RA with the IV formulation provides sufficient reassurance that a similar magnitude of effect will apply with the SC formulation.

Risks

Unfavourable effects

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

No new safety concerns were identified in the early RA patients in relation to the use of the SC formulation of TCZ.

Uncertainty in the knowledge about the unfavourable effects

The safety evaluation is also based on an unplanned analysis of subpopulations with limited overall exposure in the target early RA population to the SC formulation of TCZ. Nevertheless, given the PK comparability between the two formulations, and the overall experience with TCZ in early RA, no new safety issues should be expected with SC administration of TCZ in this population. Long term ongoing registries for TCZ as described in the risk management plan are considered adequate to provide information on the use of the SC formulation in early RA patients.

Effects Table

Table 21. Effects Table for tocilizumab SC in the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate

Effect	Short Description	Unit	TCZ 162 mg SC	TCZ 8mg /kg IV	Uncertainties/ Strength of evidence	References
Favourable Effects						
Disease remission	DAS28 <2.6 at weeks 24	%	35.6	38.6	Post-hoc analysis, small sample size Results sustained up to 2 years	WA22762 (early RA sub-population)
HAQ-QI	Decrease ≥ 0.3	%	69	84.1		
Unfavourable Effects						
Serious infections	Exposure adjusted incidence	N/100 patient-years	2.38	2.49	Limited exposure with the SC formulation in early RA. No evidence of differing safety in overall RA population and/or with IV formaultion	WA22762 (early RA sub-population)
Clinically significant hypersensitivity reactions	Exposure adjusted incidence	N/100 patient-years	0.95	3.11		
Neutropenia	Grade 3-4	N (%)	7 (6.5)	3 (4)		

Abbreviations: TCZ: tocizilizumab, SC: subcutaneous, IV: intravenous, DAS28=Disease activity score 28 joints, , HF=heart failure, NEC=Not elsewhere classified, HLT=High Level Term

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. An established treatment option for patients with adult RA is TCZ IV is now TCZ IV in combination with MTX. However IV infusion requires administration by a healthcare professional (HCP) in a clinical setting, which affects the flexibility of the patient.

The SC formulation will be a valid option for the patient, including patients with early RA (disease duration ≤ 2 years). From a medical viewpoint, bypassing the requirement for IV access is a benefit, especially important for patients with poor venous access. Additional value is also the shorter administration time and

the option to receive the treatment independent for a HCP.

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.

The safety profile of TCZ SC in patients with early RA is considered to be manageable, through the warnings in the product information and the risk minimisation activities described in the risk management plan. This has been demonstrated to be generally comparable with the safety profile of TCZ treatment in patients with RA of any duration.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

Clinical meaningful efficacy has been demonstrated for SC TCZ in patients with early RA, which is expected to be of a similar magnitude to that of patients treated with IV TCZ. No significant differences in the safety profile are to be expected between the two formulations, and the risks associated with TCZ use are adequately managed through its SmPC and risk management plan.

4. Recommendations

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:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) for the RoActemra subcutaneous formulation; as a consequence, section 4.1 of the SmPC is updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. Moreover, the MAH took the opportunity to update the contact details of the local representative in Germany in the Package Leaflet. Further, the updated RMP version 18.1 has been agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).