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SCIENTIFIC DISCUSSION

FOR
RoActemra

International non-proprietary name/Common name:
tocilizumab

Procedure No: EMEA/H/C/00955/II/0007

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

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Scientific discussion

1.1. Introduction

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

The recommended posology is 8 mg/kg body weight, but no lower than 480 mg, given once every four weeks.

This application seeks to extend the current indication to include a statement that RoActemra inhibits the progression of joint damage and improves physical function.

Study WA17823 is a randomised, controlled, double-blind, parallel group Phase III study in which adult RA patients were initially randomised to receive placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg. All patients received concomitant MTX. This study was designed to assess the reduction in signs and symptoms of RA after 24 weeks, prevention of joint damage at 52 weeks evaluated by radiographs (with confirmation at 104 weeks), physical function at 52 weeks (with confirmation at 104 weeks), and long-term safety.

During year 1, the study was conducted as a randomised, double-blind, and parallel group design. After week 52, patients were switched to open-label treatment with tocilizumab 8 mg/kg. However, patients who were responding well after one year of treatment, as indicated by a 70% improvement in joint count, could continue on their double-blind assignment rather than switching to open-label treatment with tocilizumab 8 mg/kg. Patients who chose to continue their double-blind treatment at week 52 could still switch to open-label treatment between weeks 52 and 104 (year 2) if they were no longer receiving the same level of efficacy (a 24-week interim analysis of data on the reduction of signs and symptoms of RA was included in the initial marketing authorisation application (MAA) submitted in November 2007 and approved in January 2009).

This variation includes the 2-year Clinical Study Report for WA17823; these data demonstrate that tocilizumab in combination with MTX reduced the progression of joint damage and improved physical function over 2 years. The reduction in clinical signs and symptoms of RA, demonstrated in the initial MAA, was maintained/improved over 2 years of treatment. Further supportive long-term efficacy data are provided from ongoing extension studies (WA18695/WA18696) that enrolled patients from the core Phase III trials submitted with the initial MAA (WA17822, WA17824, WA18062, WA18063) plus WP18633 (a Phase I drug-drug interaction study).

Long-term safety data are provided from Study WA17823, as well as from the ongoing extension studies (WA18695/WA18696). The overall safety profile observed in patients with prolonged exposure to tocilizumab is consistent with what has been previously characterised.

Due to the ongoing review of the safety as part of this variation application, some changes have been made to the Summary of Product Characteristics (SmPC), including changes to the posology and additional information in special warnings and precautions for use.

As part of this ongoing evaluation of the safety, plus further elucidation of the mechanism of action of tocilizumab, non-clinical studies on placental transfer and milk excretion and reproductive and developmental toxicology have been included in this variation application.

Joint destruction and physical functioning have been discussed to some extent in the initial PIP application and are considered to be covered by the existing EMA Decision P129/2009 on "Autoimmune arthritis" as per the PIP procedure EMEA-000309-PIP01-08-M01.

1.2. Non-clinical aspects

The MAH has provided new pharmacological, pharmacokinetic and toxicological information obtained with tocilizumab and its murine analogue, MR16-1, a rat anti-mouse IL-6 receptor (IL-6R) monoclonal antibody (IgG1). In order to provide a thorough non-clinical risk evaluation of any interference with IL-6R signalling and the full reproductive cycle, fertility and pre-/postnatal development studies were conducted in the mouse using MR16-1. Further, a combined fertility and pre-/ postnatal development study was conducted in IL-6 knockout mice. The pre-/postnatal development studies included a determination of T-cell subtypes and functional assessment of the immune system.

These additional non-clinical toxicity studies were conducted in compliance with the good laboratory practice (GLP) standards.

Pharmacokinetics

Determination of MR16-1 Concentration and Anti-MR16-1 Antibody Titer in Mouse Plasma in "Placental Transfer Study of MR16-1 in Mice (Study No. PBC036-072):"

A single intravenous administration of MR16-1 (50 mg/kg) was given to pregnant mice on days 11, 15 and 17 of gestation, and MR16-1 concentrations in plasma of pregnant animals and foetuses on day 18 of gestation were measured by ELISA. In addition, anti-MR16-1 antibodies in plasma of pregnant animals and foetuses dosed on day 11 of gestation were measured by ELISA.

MR16-1: Milk excretion study of MR16-1 in mice
A single intravenous administration of MR16-1 (50 mg/kg) was given to mice on days 5 to 6 after parturition, and MR16-1 concentrations in plasma and milk were measured before dosing, 1, 3 and 7 days post dose by ELISA. In addition, anti-MR16-1 antibody in plasma and milk were measured before dosing and 7 days post dose by ELISA.

Toxicology

Studies were conducted on the effects of MR16-1 on male and female fertility, and pre- and postnatal development in the mouse, including determination of immune function.

In addition, a combined fertility and pre-/postnatal development study was conducted in IL-6 knockout mice cross-paired with wild-type mice. This study also included determination of immune function parameters in the F0 and F1 generation. As the studies conducted with MR16-1 were associated with deaths of at most 24% of repeatedly treated animals, in particular at the low dose, starting after a few administrations, some further investigations were carried out to clarify the cause of these deaths. Analysis revealed that repeated treatment with MR16-1 evokes antibodies in plasma, i.e. plasma samples judged as positive for anti-MR16-1 antibodies, were also positive for extravasation in the cutaneous anaphylaxis test. It was concluded that this antibody development likely has led to fatal immunogenic reactions of at most ~24% of the recipient animals.

Reproductive and Developmental Toxicity

MR16-1: A Study for Effects of MR16-1 on Fertility and Early Embryonic Development to Implantation by Intravenous Administration in Male Mice (study 1033493)
A rat IgG1 antibody directed against mouse IL-6R resulted in the death of 10 out of 57 males in the 15-mg/kg group starting after several administrations and recorded mostly 20-70 minutes after administration. These animals very likely died due to a decreased blood flow, i.e. pulmonary stasis

resulting from an immunoreaction to MR16-1. No adverse effects were observed in terms of body weight, food consumption, gross pathological findings, testis or epididymis weights, or histopathological findings of the testis or epididymis in any treatment group.

MR16-1: A Study for Effects of MR16-1 on Fertility and Early Embryonic Development to Implantation by Intravenous Administration in Female Mice (study 1033494)

Rat IgG1 antibody directed against mouse IL-6R resulted in the death of 12 out of 60 females in the 15-mg/kg group and 1 out of 60 female in the 50-mg/kg group starting after a few administrations and recorded mostly 30-60 minutes after administration. These animals very likely died due to a decreased blood flow, i.e. pulmonary stasis resulting from an immunoreaction to MR16-1. No adverse effects were observed in terms of body weight, food consumption, estrous cycles, or gross pathological findings in any treatment group.

MR16-1: A Study for Effects of MR16-1 on Pre- and Postnatal Development, Including Maternal Function, by Intravenous Administration in Mice (study 103492)

Rat IgG1 antibody directed against mouse IL-6R resulted in the death of 11 out of 66 dams in the 15-mg/kg group only starting after a few administrations and recorded mostly within 2 hours after administration. These animals very likely died due to a decreased blood flow, i.e. pulmonary stasis resulting from an immunoreaction to MR16-1. Additionally, abortion in 3 dams and total F1 litter loss in 3 dams, and suppression of body weight gain and decreases in food consumption in dams and decreased pup viability by Day 4 after birth, which were also likely due to an immunoreaction to MR16-1, were observed in the 15-mg/kg group only. In the 50-mg/kg group, no dams died, and no adverse effects were observed in terms of clinical signs, body weight, food consumption, delivery, nursing behaviour, or gross pathological findings.

Combined Fertility and Prenatal/Postnatal Reproduction Toxicity Study in B6.129S2-Il6tm1Kopf/J (IL-6 knockout) and C57 Mice, Including Behavioural/Functional Evaluations (study 1029892)

The study was designed to detect effects on the estrous cycle, tubal transport, implantation, gestation, parturition, lactation and maternal behaviour in female mice, and permit detection of functional effects (e.g., effects on libido or epididymal sperm maturation) not detected by histological examinations of male mouse reproductive organs, and to provide data on immunocompetence and immunophenotyping from cross pairing of male and female B6.129S2-Il6tm1Kopf/J (IL-6 knockout) and C57 Mice. Because manifestations of effects induced during this period may be delayed in the offspring, observations were continued through sexual maturity of F1 generation mice.

Discussion on the non-clinical aspects

Several studies were designed in order to investigate the effects of intravenous treatment with MR16-1, a rat IgG1 antibody directed against mouse IL-6 receptor, on pre- and postnatal development including assessment of immune function. There is published evidence that the pharmacological properties of MR16-1 with tocilizumab are similar. Furthermore the specificity of the rat MR16-1 antibody for the mouse IL-6 receptor was demonstrated.

The data show that MR16-1 was transferred across the placenta from dams to foetuses in pregnant mice and that MR16-1 was excreted in milk after intravenous administration of MR16-1 to lactating mice.

Studies on male and female fertility in the mouse revealed that repeat dosing with MR16-1 was associated with deaths of at most 24% of treated animals. It can be agreed that these deaths might be attributed to high immunogenic potential of the rat antibody in mice. From the other data (peripheral blood phenotypes, primary IgM or IgG antibody responses, clinical signs, body weight, food consumption, gross necropsy etc.) there was no clear significant evidence for toxicologically relevant impairment of reproductive and developmental functions including the developing immune system. As tocilizumab is of very low immunogenicity in humans, these immunological reactions of mice towards

repeated treatment with the rat IgG1 antibody MR16-1 can be considered as not relevant for the human situation.

The MAH provided a thorough critical reassessment of the non-clinical data regarding the observations made in the combined fertility and pre/postnatal development study with IL-6 knock out mice such as female mice (F0) sacrificed or dying prior to scheduled euthanasia., decreased pup survival on days 2 to 4 postpartum, slower learning ability of IL-6 knock-out mice versus C57 mice and a critical assessment of the findings in relationship to immunological parameters determined in the study.

Regarding the number of female mice sacrificed or dying prior to scheduled euthanasia, still no explanation for the deaths has been provided but the MAH clarified that there were no such findings in the pre-postnatal study with the IL6R surrogate antibody MR16-1 and that the use of RoActemra in humans in late stages of pregnancy is indicated only under favourable risk-benefit conditions.

Regarding the decreased pub survival, differences between the in-bred strains and the out bred strain were identified as cause. Differences between knockout and wild-type mouse strains in other reproductive parameters were published in literature.

There were some differences in the F0 IL-6 knock out animals versus their wild type counterparts described in the study report. Upon a closer look at the individual data as part of the immunology report only the cell-mediated immunity appears to be decreased in male F0 animals.

Finally fertility and pre/postnatal studies with MR16-1 in mice did not show any impairment of pregnancy or parturition, or harm to offspring during the pre- and postnatal development phase with treatment from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behaviour, learning ability, immune competence and fertility of the offspring.

3.3 Clinical aspects

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

3.3.1 Clinical pharmacology

Pharmacokinetics

This application includes the report of routine pharmacokinetic sampling throughout the two year period in study WA17823. A total of 841 patients provided PK samples as per the protocol. The mean (range) age of patients was 53 (19-85) years and the mean (range) weight was 71.6 (34.5-148) kg. There were more females (83%) than males (17%) in this PK population.

Two further pre-dose levels of tocilizumab (Ctrough) have been measured in year 2 (time points: week 80 and 104). The mean predose concentrations at weeks 80 and 104 are summarized in Table 1. For comparison, the mean predose TCZ concentrations at weeks 24 and 52 (year 1) are also summarized in Table 1. The mean steady-state predose concentration of TCZ for those receiving 4 mg/kg was 0.567 ± 1.80 µg/mL at week 80 and 1.09 ± 2.77 µg/mL at week 104**.** The mean steady state predose concentration of TCZ for those receiving 8 mg/kg was 18.5 ± 13.2 µg/mL at week 80 and 19.9 ± 17.0 µg/mL at week 104.

Table 1 **Summary of TCZ Predose Concentrations (µg/mL)**

	Year 1		Year 2	
Dose, mg/kg	Week 24	Week 52	Week 80	Week 104
4 mg/kg				
N	361	344	67	56
Mean± SD	1.02 ± 6.14 (602)	0.695 ± 2.02 (291)	0.567 ± 1.80 (318)	1.09 ± 2.77 (254)
Median	0	0	0	0
Min-Max	0 - 98.3	0 - 17.0	0 - 11.2	0 - 10.7
8 mg/kg				
N	350	391	644	595
Mean± SD	15.9 ± 12.0 (76)	17.6 ± 15.3 (87)	18.5 ± 13.2 (72)	19.9 ± 17.0 (86)
Median	14.2	15.5	16.8	17.1
Min-Max	0 - 85.0	0 - 193	0 - 93.5	0 - 249

The concentrations of TCZ were sustained from week 24 in year 1 to week 104 (Table 1), which is at the end of year 2.

Dosing by body weight / PK/PD relationship

TCZ concentration versus response

The use of TCZ 8 mg/kg has been demonstrated as an effective regimen both as monotherapy and in combination with MTX/other DMARDs. The influence of body weight on systemic clearance supports the dosing of TCZ on a milligram per kilogram basis in the majority of patients.

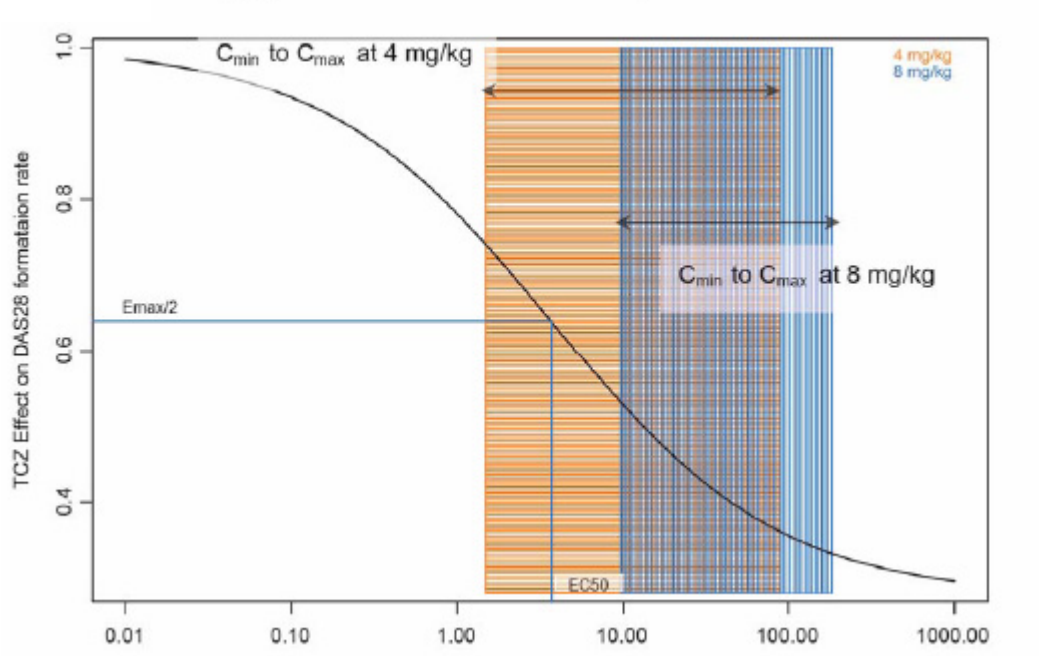
From the population PK analysis included in the original submission it is known that TCZ-treated patients with high body weight have higher AUC, Cmax, and Cmin values compared to patients with low body weight, who have relatively lower AUC, Cmax, and Cmin (Table 2).

Table 2 **Secondary PK Parameters (Mean ± SD) at Steady-State by Category of Body Weight with a Body Weight-Based Dosing Regimen**

PK Parameter	Body Weight Category (kg)			
	< 60	60–80	80–100	≥ 100
Patient N (% of total)	395 (22%)	817 (46%)	418 (23%)	163 (9%)
4 mg/kg				
AUC (10^3 µg·h/mL)	10.4 ± 2.8	13.2 ± 3.5	16.6 ± 4.6	21.4 ± 5.4
C_{max} (µg/mL)	68.7 ± 16.3	82.5 ± 19.0	101 ± 21	128 ± 27
C_{min} (µg/mL)	1.01 ± 1.0	1.37 ± 1.22	2.02 ± 2.11	2.93 ± 2.50
8 mg/kg				
AUC (10^3 µg·h/mL)	29.8 ± 8.3	36.7 ± 10.2	44.6 ± 12.8	55.5 ± 14.1
C_{max} (µg/mL)	145 ± 35	174 ± 41	213 ± 47	269 ± 57
C_{min} (µg/mL)	8.99 ± 7.17	12.0 ± 8.6	15.1 ± 11.3	19.4 ± 11.8

A sigmoid Emax model was developed to describe the relationship between TCZ concentrations and reduction in DAS28 observed from the clinical data in the 6-month controlled studies (Figure 1). The EC50 (the concentration at which a DAS28 reduction was achieved that is 50% of the maximal response) was approximately 3.72 µg/ml. For the TCZ 8 mg/kg dose, the majority of patients were above the EC50. When TCZ serum concentrations were greater than 19.4 µg/ml (the mean Ctrough at steady state, following TCZ 8 mg/kg q4w, see Table 2), TCZ had already achieved 84% of its maximal effect on the decrease in DAS28. The dose response curve flattens with increasing TCZ concentrations; thus only minor gains in efficacy will be achieved for each incremental increase in TCZ concentration (Table 2 and Figure 1).

Figure 1 **E_{max} Model for DAS28 – TCZ Exposure**



The CHMP noted that the TCZ effect approached the plateau of the response curve at 8 mg/kg dose (Cmin to Cmax) and that further increase of exposure would result in minimal reduction in DAS formation rate.

Response in different body weight groups

The impact of weight on clinical response (ACR20) was explored using 6 month data from the pooled DMARD-inadequate responder population in the original submission. The greatest response was seen in patients with a body weight < 60 kg. Overall, the response to TCZ 8 mg/kg + DMARD was shown to decrease slightly with increasing body weight; ACR20 response rates were 65%, 58%, and 50% in the < 60 kg, 60–100 kg, and > 100 kg subgroups, respectively.

Long-term follow-up was performed with the All Exposure population (intent to treat (ITT) population) from the open-label extension studies. In this analysis, ACR response rates by body weight were evaluated in four subgroups of patients by baseline weight (< 60 kg, 60 to < 80 kg, 80 to 100 kg, and > 100 kg). Results confirmed previous findings, which indicated that the best responses were observed in patients who were < 60 kg and that, as patient weight increased, the response to TCZ therapy slightly decreased.

After 48 weeks of treatment, ACR50 response rates in the < 60 kg subgroup were 50%, 42%, and 47% for patients from the WA17824, WA18062, and Pooled groups, respectively. In contrast, mean ACR50 responses for patients in the > 100 kg subgroup were 35%, 33%, and 39%. After 96 weeks of treatment, patients < 60 kg continued to show greater improvement in ACR50 response (59%, 55%, and 57% for the respective groups), compared with responses in the > 100 kg group (39%, 41%, and 44%).

Patients weighing less than 60 kg had the highest efficacy in both the 6-month studies and in long-term follow-up in the All Exposure population. Thus, the overall exposure to TCZ in this group is sufficient, indicating that a minimum dose of 480 mg is not required. The SmPC has been updated accordingly.

To further illustrate the relationship between exposure and efficacy in patients with a body weight > 100 kg, model-based simulations were performed. The simulations compared two dosing regimens: TCZ 8 mg/kg versus a capped dose of 800 mg in patients with body weight > 100 kg. The results indicated that the proportion of patients > 100 kg predicted to have DAS28 remission following TCZ 8 mg/kg (39.8%) was comparable to that for the dose capped at 800 mg (38.5%). Similarly, the proportion of patients predicted to have good EULAR response following TCZ 8 mg/kg (50.5%), was comparable to that for the dose capped at 800 mg (48.8%).

The difference in the response to a TCZ dose of 8 mg/kg compared with a total dose of TCZ 800 mg thus appears to be small, with no major clinical impact on efficacy. These results confirm that capping the dose at 800 mg for patients with body weight > 100 kg will not limit the efficacy in this population.

These analyses by body weight showed that, although exposure increased as patient weight increased, the response to TCZ therapy did not increase. These finding can be explained by the Emax relationship between TCZ concentration and efficacy parameters (see Figure 1). Simulated response data confirm that administration of the maximum total dose of 800 mg results in response levels that are comparable to those obtained with the dose of 8 mg/kg. Specifically these data show that patients weighing more than 100 kg, who would receive a total dose exceeding 800 mg, do not derive benefit proportional to the increase in exposure. The SmPC has been updated accordingly.

Safety in different Body weight groups

Weight

In the All Control population, the rate of serious infections was higher in patients weighing > 60 kg and treated with TCZ 8 mg/kg, with the greatest increase observed in patients weighing > 100 kg.

In the All Exposure population, the rate of serious infections was 3.3 per 100 patient-years for patients < 60 kg, 4.2 per 100 patient-years for patients ≥ 60 to < 80 kg, 5.0 per 100 patient-years for patients ≥ 80 to < 100 kg, and 8.5 per 100 patient-years for patients ≥ 100 kg.

BMI

In the All Control population, patients with very low (< 18.5) or very high (≥ 30) BMI and treated with TCZ 8 mg/kg reported the highest rate of serious infections.

In the All Exposure population, the rate of serious infections was 4.4 per 100 patient-years for patients with a BMI < 18.5, 3.2 per 100 patient-years for patients with a BMI ≥ 18.5 to < 24.9 kg, 4.4 per 100 patient-years for patients with a BMI ≥ 25 to < 29.9, and 6.2 per 100 patient-years for patients with a BMI ≥ 30.

Discussion on dosing by body weight/PK/PD relationship

The use of TCZ 8 mg/kg has been demonstrated as an effective regimen both as monotherapy and in combination with MTX/other DMARDs. The influence of body weight on systemic clearance supports the dosing of TCZ on a milligram per kilogram basis in the majority of patients.

From the population PK analysis included in the original submission it is known that TCZ-treated patients with high body weight have higher AUC, Cmax, and Cmin values compared to patients with low body weight, who have relatively lower AUC, Cmax, and Cmin.

It is agreed that the TCZ effect approached the plateau of the response curve at 8 mg/kg dose (Cmin to Cmax) and that further increase of exposure would result in minimal reduction in DAS formation rate.

Long-term follow-up results confirmed previous findings that the best responses were observed in patients who were < 60 kg and that, as patient weight increased, the response to TCZ therapy slightly decreased. Although exposure increases as patient weight increased (e.g. AUC in patients weighing > 100 kg is 55000 compared to 36000 in the 60-80 kg subgroup), the response to TCZ therapy does not increase proportionally. This is in agreement with the sigmoidal concentration-response relationship evaluated. Simulated response data confirmed that administration of the maximum total dose of 800 mg in patients weighing > 100 kg results in response levels that are comparable to those obtained with the dose of 8 mg/kg. This means that capping the dose at 800 mg for these patients will not limit the efficacy in this population. The rate of serious infections per 100 patient years after TCZ 8 mg/kg increases by body weight from 3.4 to 10. This is in accordance with the increase in TCZ exposure (AUC, Cmax and Cmin) by body weight since there is a relationship between TCZ concentration and neutrophil loss rate. This indicates that the subgroup > 100 kg bears the highest risk for infections. Since no increase in response is observed in this group this finding supports the proposed capping of the dose at 800 mg.

Since patients weighing less than 60 kg had the highest efficacy in both the 6 month studies and in long-term follow-up in the All Exposure population, the overall exposure to TCZ in this group appears to be sufficient, indicating that a minimum dose of 480 mg is not required.

The current safety data also indicate the trend on increased incidence of serious infections in patients with low BMI (<18.5) without such finding in patients with <60 kg of weight. The MAH has provided a conclusive overview of the data regarding the connection between low body weight/ low BMI and the possibly increased risk of serious infection. No direct link between low BMI and higher risk can be assumed but the number of concomitant diseases and underlying risk factors should lead to a cautious treatment with RoActemra.

3.3.2 Clinical efficacy

The clinical data presented in support of the current application derive from a planned interim analysis of 1 year radiographic and physical function data, confirmed with results from an analysis of 2 year data from study WA17823. This application is further supported by cumulative long-term efficacy and safety data from the open-label extension phase of study WA17823 and the two ongoing open label extension studies (WA18695 and WA18696), which include patients from the core studies in the original application.

The cumulative long-term clinical database includes patients from controlled studies WA17822, WA17823, WA17824, WA18062, WA18063 and WP18663 who received at least one dose of TCZ, regardless of whether or not they entered long-term extension studies WA18695 or WA18696 or continued into the extension phase of study WA17823. For the long-term evaluation of efficacy, data from TCZ treated patients in these studies are pooled with the data from the extension phase of WA17823 and the extension studies WA18695 and WA18696. Up to the cut-off date for this submission, the 4009 patients included in this population provide a total of 8579.7 patient-years exposure to TCZ, with over 1000 patients treated for 156 weeks (3 years). This is referred to as the All Exposure population and is the primary population for the assessment of long-term safety and efficacy of TCZ.

A subset of this population, comprising only data from double-blind controlled trials, was also analyzed for safety. This analysis censors the data from the point that a patient changes treatment regimen. Change in treatment regimen includes: entering escape therapy, changing TCZ dose, or switching to open label TCZ. This is referred to as the All Control population. Under controlled conditions in the Phase III studies, 1555 patients received control treatment, 774 patients received TCZ 4 mg/kg, and 1870 patients received TCZ 8 mg/kg.

Main study

WA17823

Study WA17823 was a phase III, multi-centre, randomized, double-blind, placebo controlled, parallel group study in patients with moderate to severe RA who had an inadequate response to MTX. Patients were randomized to receive study drug (TCZ 4 mg/kg, TCZ 8 mg/kg, or placebo) in combination with MTX in year 1, followed by open-label treatment with TCZ 8 mg/kg + MTX in year 2. The study was designed to assess TCZ therapy in combination with MTX versus MTX alone with respect to safety, reduction in signs and symptoms of RA after 6 months, prevention of joint damage at one year (with confirmation at two years), and improvement in physical function at one year (with confirmation at two years). The interim analysis of 24-week data, which demonstrated the safety and efficacy of TCZ in reducing the signs and symptoms of RA, was reported in the initial MAA.

Eligible patients were randomized on a 1:1:1 basis to one of the following treatment groups:

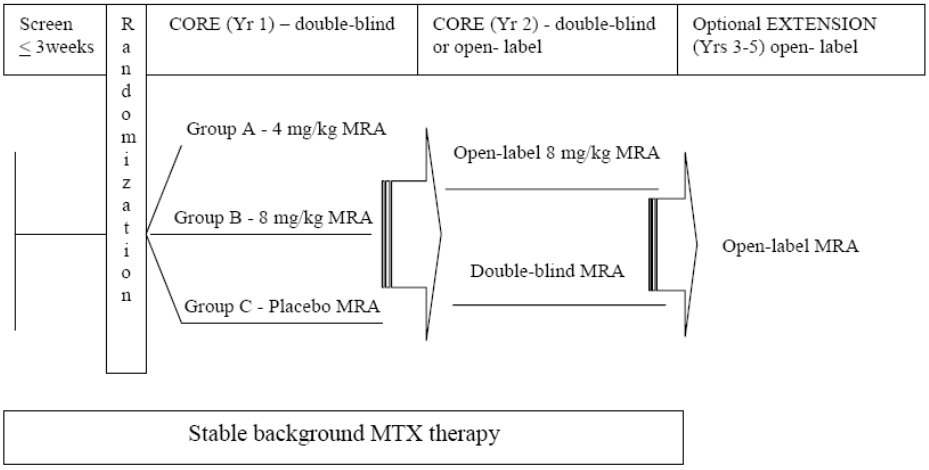
•**Group A:** TCZ 4 mg/kg intravenously (iv) every 4 weeks (q4w) in combination with MTX (10 to 25 mg orally or parenterally) weekly

•**Group B:** TCZ 8 mg/kg iv q4w in combination with MTX (10 to 25 mg orally or parenterally) weekly

•**Group C:** Placebo iv q4w in combination with MTX (10 to 25 mg orally or parenterally) weekly

Figure 2

Overview of Study Design for WA17823



Patient Population

A total of 1196 patients were enrolled in study WA17823. Patients were recruited at multiple centres worldwide: 41% from Europe, 40% from North America (27% from the USA), 10% from Brazil, 5% from South Africa, and 4% from China.

The patient disposition for the 1190 patients randomized to treatment was as follows: 393 placebo; 399 TCZ 4 mg/kg; and 398 TCZ 8 mg/kg.

The patients in study WA17823 were selected as moderate to severely active RA patients with erosive joint disease; to be enrolled in the study they had to have radiographic evidence of at least one joint with definite erosion attributable to RA, as determined by the central reading site.

Certain subpopulations were excluded from the study, such as pregnant or lactating women, patients with renal impairment, and patients with liver disorders. The majority of patients were recruited in North America, Europe and South/Central America. At study entry, patient ages ranged from 18 to 84 years (median 51 to 54 years) across the treatment groups.

After week 52, patients were required to switch to open-label treatment with 8 mg/kg TCZ, unless they were maintaining a very good response (> 70% improvement in swollen joint count (SJC)/tender joint count (TJC). The proportion of patients who made this switch ranged from 62% to 68% of patients across the three treatment groups. Fifteen (15) percent of placebo patients and 22% of TCZ patients (both doses) qualified to continue on double-blind treatment at week 52.

At 104 weeks, 73% of patients originally randomized to placebo and 78% of patients originally randomized to TCZ (both dose groups) completed the core study. Approximately 10% to 13% of the originally randomized patients were receiving double-blind treatment at this time; the remaining patients were receiving open-label TCZ 8-mg/kg treatment.

Dose and Dosing Regimen

Doses investigated in the Phase III studies, including study WA17823, were selected on the basis of safety and efficacy data from the Chugai 16-week Phase II dose-ranging study LRO301 in MTX inadequate responders. This study included TCZ doses of 2, 4, and 8 mg/kg of TCZ given alone or in combination with MTX. Based on the positive outcome of these studies, TCZ doses of 4 and 8 mg/kg were explored in the MAH's Phase III studies. A 4-weekly dosing interval was primarily chosen based on data from the same study demonstrating clinical improvements at 2 and 4 weeks after an infusion of TCZ.

During year 1 of the core study, patients received an infusion of TCZ or placebo q4w in a blinded fashion for a total of 13 infusions. Patients who failed to respond to treatment (i.e., achieved less than a 20% improvement in both the SJC and tender joint count TJC) after 16 weeks of blinded therapy were offered escape therapy with TCZ.

Year 2 of the core study started after completion of 52 weeks of treatment. Patients who completed 52 weeks of double-blind treatment, or received TCZ escape therapy in year 1, received open-label treatment with 8 mg/kg TCZ infusions q4w for 12 months in year 2 of the study. However, patients doing well on blinded therapy at week 52 (defined as showing ≥ 70% improvement from baseline in SJC and TJC at two consecutive visits [weeks 48 and 52]) were allowed to continue on their current treatment in year 2 in a blinded fashion. The treatment blind was maintained until the last patient completed the week 52 visit and the clinical study database for year 1 was locked. Patients could switch to open-label treatment with TCZ 8 mg/kg at any time until week 104.

Endpoints

The co-primary endpoints in study WA17823 at weeks 52 and 104 were:

• the change from baseline in total Sharp-Genant score and,

• the change the change in physical function at weeks 52 and 104, measured by the area under the curve (AUC) for the change from baseline in HAQ-DI.

Radiographs of each hand and wrist (posterior anterior) and each foot (anterior posterior) were taken at specified time points. Radiographs were read in two reading campaigns. Campaign 1 included evaluations of the baseline, week 24, week 52, and early withdrawal or escape therapy readings taken up to the week 52 visit. Campaign 2 included evaluations of the baseline, week 24, week 52, week 80, week 104, and early withdrawal or escape therapy readings taken up to the week 104 visit. Campaign 1 assessments were used for the year 1 analysis; those of campaign 2 were used for the year 2

analysis. The data from the different campaigns were not mixed for a given patient. The primary radiographic endpoint was the change from baseline in total Sharp-Genant score at weeks 52 and 104.

Supporting Studies (WA18695, WA18696, and WA17823 Long-Term Extension Studies)

The primary objective of these studies is to assess the long-term safety of TCZ 8 mg/kg as monotherapy or in combination with background DMARDs therapy with regard to adverse events and laboratory result abnormalities. Secondary objectives include assessment of continuing clinical benefit using the same measures as in the core studies. Efficacy parameters were assessed every 12 weeks in WA18695 and WA18696, and every 8 weeks in study WA17823. Data for these patients were included in this summary up to the cut off point of February 6, 2009.

Table 3 **Overview of the Supporting Phase III Open-Label Extension Studies**

Study/ No. of Pts Randomized	Patient Population	Primary Endpoint	Design and Duration	Treatment	Escape Therapy
WA18695 **N = 537**	Patients completing treatment in WA17822	Long-term safety/efficacy	OL extension study; 5 yrs*	**1 arm study**: TCZ 8 mg/kg iv q4w + MTX	N/A
WA18696 **N = 2066***	Patients completing treatment in WA17824, WA18062, WA18063, WP18663	Long-term safety/efficacy	OL extension study; 5 yrs*	**1 arm study**: TCZ 8 mg/kg iv q4w alone or + MTX or other DMARD(s)	N/A
WA17823 (yrs 3 to 5) N =1196	Patients completing treatment in the 2-yr core study period of WA17823	Long-term safety/efficacy	OL extension phase; up to 3 yrs	**1 arm study**: TCZ 8 mg/kg iv q4w + MTX or other DMARD(s)	N/A

Abbreviations: iv = intravenous, N/A = not applicable, OL = open label, q4w = every 4 weeks.
* Patients were not randomized into WA18695 and WA18696, but enrolled from studies WA17822, WA18063, WA18062, WA17824, and WP18663.

The efficacy analyses for the supporting studies were performed on the All Exposure population, consisting of all patients from the core studies (WA17822, WA17823, WA17824 [including the transition phase], WA18062, WA18063) who received at least one dose of active TCZ, regardless of whether they entered an extension study, and those from the WA17823, WA18695, and WA18696 extension studies. (Note: study WP18663 was a phase 1 study with no efficacy endpoints; efficacy data for patients initially enrolled into WP18633 became available only when those patients entered WA18696).

Results

Study WA17823

Results at Week 52

Treatment with TCZ 4 mg/kg and 8 mg/kg + MTX reduced the rate of prevention joint damage (PJD) compared with placebo + MTX, as demonstrated by the change in Total Sharp Score TSS at year 1 ($p \leq 0.0001$ for both comparisons versus placebo). While the primary analysis compared the entire distribution, the mean values were 0.34, 0.29, and 1.13 for the TCZ 4 mg/kg, TCZ 8 mg/kg, and placebo groups, respectively. The reduction in PJD was driven mainly by a statistically significant change ($p \leq 0.0001$ for both comparisons) in erosion score (mean change of 0.21 for TCZ 4 mg/kg and 0.17 for TCZ 8 mg/kg versus 0.71 for placebo). Joint space narrowing scores also showed statistically significant improvement with TCZ 4- and 8-mg/kg therapy as compared with placebo ($p < 0.05$ for both comparisons; mean change in JSN score of 0.13 and 0.12 versus 0.42, respectively). The robustness of the primary analysis was supported by a number of sensitivity analyses confirming a significantly lower rate of PJD in the TCZ-treated groups as compared with placebo.

Treatment with TCZ was also associated with a significantly greater proportion of patients with no radiographic progression over one year compared with the placebo + MTX group (80.5% for TCZ 4 mg/kg and 84.5% for TCZ 8 mg/kg compared with 67.2% for placebo).

A statistically significant improvement in physical function, as assessed by the co-primary functional endpoint HAQ-DI AUC, was observed for patients receiving TCZ (both doses) compared with placebo.

In addition, the proportion of patients with a clinically important change in HAQ-DI (decrease from baseline by 0.3) was significantly greater for patients receiving TCZ 8 mg/kg + MTX than for patients receiving placebo + MTX. The proportions of patients achieving ACR20, ACR50 and ACR70 responses at week 52 were significantly greater in both TCZ groups compared with the control group. Moreover, the proportion of patients in the TCZ groups who achieved a major clinical response (defined as achievement of ACR70 response for ≥ 6 months) (4.0% and 6.5% for the 4- and 8-mg/kg groups, respectively) differed significantly from that of the placebo group (0.5%; $p = 0.0010$ and $p < 0.0001$).

Both TCZ-treated groups showed a greater decrease in DAS28 scores compared with the control group; the mean change from baseline for the 8-mg/kg group differed significantly from that for placebo ($p < 0.0001$). By week 52, nearly half (47%) of TCZ 8 mg/kg patients achieved remission (DAS28 < 2.6) compared with 8% of placebo patients.

Results at Week 104

For the year 2 analyses, patients were included in the groups to which they were initially randomized. It is important to note that, due to the study design, the majority of patients in the placebo group received escape treatment (TCZ 4 mg/kg or 8 mg/kg) in year 1, and in the TCZ 4-mg/kg group, the majority of patients received treatment with TCZ 8 mg/kg for at least 12 months through year 2.

Disposition of Radiographic Data

In the ITT population at week 104, 1147 patients (96%) had a baseline and at least one post-baseline radiographic assessment. A total of 915 patients (77%) had a baseline and a week 104 radiograph (293/393 [75%] of placebo patients, 311/399 [78%] of patients on TCZ 4 mg/kg, and 311/399 [78%] of patients on TCZ 8 mg/kg).

The primary analysis, which censored post-escape and post-withdrawal data, included x-ray assessments for 75% of placebo patients (294/393), 86% of patients (343/399) on TCZ 4 mg/kg and 89% of patients (353/398) on TCZ 8 mg/kg. Of those patients, 140 in the placebo group, 231 in the 4-mg/kg group and 252 in the 8-mg/kg group had both a baseline and a week 104 radiograph and, therefore, represented the observed change. The number of patients who had their week 104 results imputed using linear extrapolation included 154, 112, and 101 patients in the placebo and TCZ 4-mg/kg, and 8-mg/kg groups, respectively. Data for these patients were imputed because their observed week 104 data were set to missing (escape or post-withdrawal data) (95, 49 and 37 patients), or because they were truly missing (includes early withdrawals for patients with no post-withdrawal data) at week 104 (59, 63 and 64 patients.

Key Findings for efficacy

Both of the co-primary endpoints for WA17823 were met at week 104. Initial treatment with TCZ 4 mg/kg and 8 mg/kg + MTX significantly reduced the rate of progression of joint damage compared with placebo + MTX, as demonstrated by the change in TSS at year 2 ($p \leq 0.025$ for both comparisons versus placebo). A significantly greater proportion of patients in the TCZ 8 mg/kg group had no progression of joint damage (change from baseline ≤0 TSS) at the end of year 2 compared with those randomized to placebo, as assessed by the change in TSS (75% and 83% in the 4-mg/kg and 8-mg/kg groups, respectively, vs. 66% for patients randomized to placebo; $p = 0.024$ and $p < 0.0001$, respectively). Moreover, the proportion of non-progressors was greater in the second year for all three treatment groups (with post-withdrawal and escape data included), including patients originally randomized to placebo (most of whom were receiving TCZ 8 mg/kg at this time), as compared to that observed at the end of year 1. Results for all radiographic endpoints at week 104 showed maintenance of effect or further improvement in the benefits obtained in the first year of the study.

At week 104, the adjusted mean change from baseline in HAQ-DI AUC (co-primary endpoint) was significantly greater for both TCZ groups as compared with the placebo group ($p < 0.0001$). Analysis of categorical changes in HAQ-DI scores at week 104 showed that over 62% of patients randomized to TCZ 8 mg/kg improved by ≥ 0.3units, showing maintenance of the year 1 levels. Additionally, the proportion of patients showing a minimum clinically important difference in HAQDI (defined as ≥ 0.25) was maintained or improved slightly from the year 1 levels.

The ACR20/50/70 response rates achieved in year 1 were maintained throughout year 2. Moreover, at week 104 the proportion of patients achieving a major clinical response in the TCZ groups increased more than 2-fold from the week 52 levels (11.5% and 14.3% of patients in the 4- and 8-mg/kg groups, respectively).

Mean DAS28 scores continued to decrease for all treatment groups. At week 104, the mean score for the 8 mg/kg group exceeded the DAS28 threshold for clinical remission (mean score of 2.55), while scores for both the placebo and 4-mg/kg groups approached that threshold (2.75 and 2.81, respectively, with post withdrawal/ escape data included). Approximately half (48%) of the patients treated with TCZ 8 mg/kg and 31% of those treated with 4 mg/kg achieved DAS 28 remission at week 52; these proportions increased to 65% and 55%, respectively, at week 104.

Progression of Joint Damage

Patients enrolled in study WA17823 had low radiographic progression rates at baseline; mean annualized progression rates were 4.19, 4.31, and 4.09 in the placebo + MTX, TCZ 4 mg/kg + MTX, and TCZ 8 mg/kg + MTX, respectively.

The proportions of patients with a radiograph at both baseline and week 52 were 83%, 89%, and 84% in the placebo + MTX, TCZ 4 mg/kg + MTX, and TCZ 8 mg/kg + MTX groups, respectively. At week 104, the proportions of patients with a radiograph both at baseline and week 104 remained high at 75%, 78%, and 78% for the respective groups.

Treatment with TCZ + MTX significantly reduced the progression of joint damage compared with placebo + MTX, as assessed by the change in total Sharp-Genant score at year 1 with a 74% and 70% inhibition of progression in the TCZ 8 mg/kg + MTX and TCZ 4 mg/kg + MTX groups, respectively, when compared with placebo + MTX.

This significant reduction in the progression of joint damage was confirmed following 2 years of treatment. The data at year 2 reflect an 81% and 70% inhibition of progression in the TCZ 8 mg/kg and 4 mg/kg groups, respectively, when compared with placebo.

The changes in total Sharp score were also supported by the changes in both erosion and joint space narrowing scores.

Table 4 **Radiographic Mean Changes at 52 and 104 Weeks in Study WA17823, Linear Extrapolation Method (ITT Population)**

	Placebo + MTX	TCZ 8 mg/kg + MTX
Changes from baseline to Week 52		
N	294	353
Total Sharp-Genant score	1.17	0.25
Erosion score	0.76	0.15
JSN score	0.41	0.10
Change from week 52 to week 104		
N	294	353
Total Sharp-Genant score	0.79	0.12
Erosion score	0.48	0.07
JSN score	0.31	0.05

Differences in the change from baseline in the total Sharp score among the three treatment groups became evident as early as week 24, when patients treated with TCZ 8 mg/kg + MTX or TCZ 4 mg/kg + MTX had a significantly smaller change compared with patients treated with placebo + MTX. Between weeks 24 and 52, patients treated with TCZ + MTX continued to have smaller changes in total Sharp score than patients treated with placebo. At week 52, when the majority of patients switched to open-label treatment with TCZ 8 mg/kg + MTX, the slope of the line for patients initially treated with placebo + MTX decreases, indicating that these patients had a smaller change in total Sharp score during the second year of treatment compared with the first. For patients initially treated with TCZ 4 mg/kg + MTX, the slope of the line at week 52 continues in an approximately linear fashion, indicating that these patients continue to experience a change in total Sharp score during year 2 that is similar to the change in year 1. For patients originally randomized to TCZ 8 mg/kg + MTX, the slope of the line at week 52 decreases slightly, suggesting that these patients experience even less of a change in total Sharp score during year 2. Similar results were seen in the sensitivity analysis including post-escape and post withdrawal data, which confirm the findings of the primary analysis.

Figure 3 **Mean Change from Baseline by Visit up to Week 104 in Total Sharp-Genant Score: Linear Extrapolation (ITT Population)**

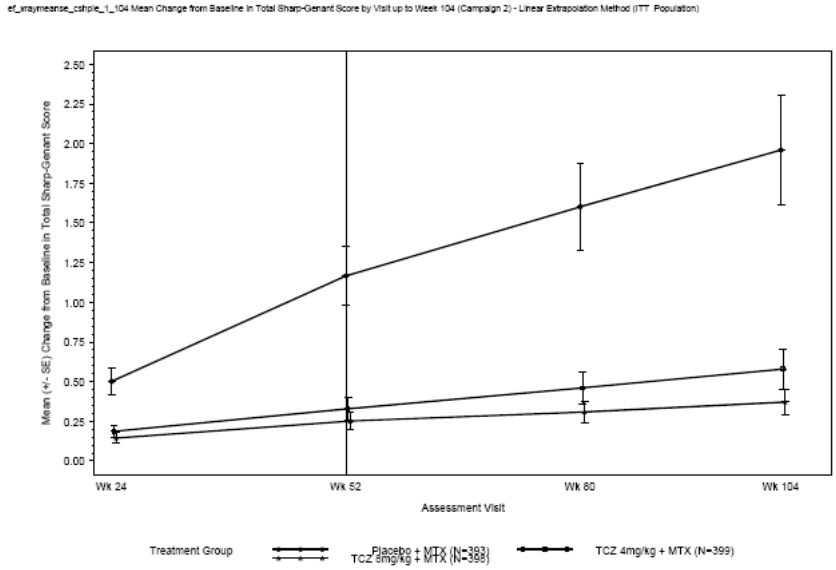
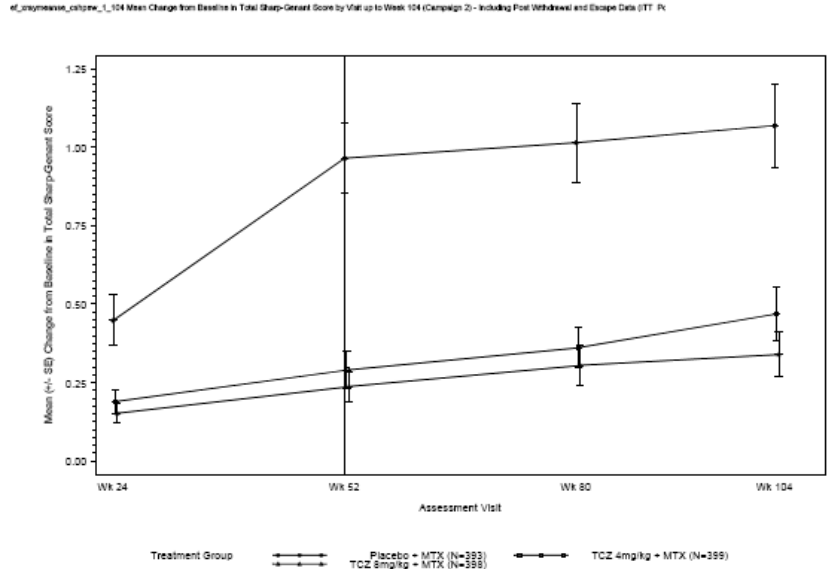


Figure 4 **Mean Change from Baseline by Visit up to Week 104 in Total Sharp-Genant Score: Including Withdrawal and Escape Data (ITT Population)**



The vertical reference
Data collected after
Campaign 2 consists of th
Program : $PRC
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The proportion of patients with no radiographic progression (defined as ≤ 0 in total Sharp-Genant score) was greater in the TCZ groups (78.1% and 83.3% in the 4- and 8-mg/kg + MTX groups, respectively) compared with the placebo + MTX group (65.6%) at week 52. These results were maintained at week 104 with significantly greater proportions of patients with no progression in total Sharp score in the TCZ 4 mg/kg + MTX (74.6%, p=0.0239) and TCZ 8 mg/kg + MTX (82.7%, p<0.0001) groups compared with the placebo + MTX group (66.3%). Similar results were observed

when considering the proportion of patients with no progression in erosion or joint space narrowing scores.

Annualized Rates of Progression

The exploratory analysis to compare the annualized progression rates for TSS, erosion and JSN scores suggested that patients randomized to TCZ 8 mg/kg who received more than 1 year of treatment experienced significantly less structural damage in year 2 compared to year 1 (rate of progression for TSS 0.07 vs. 0.24 [p<0.0001]; erosion 0.04 vs. 0.13 [p = 0.0007]; JSN 0.04 vs. 0.11 [p = 0.0002]). Similarly, rates of progression in year 2 for patients randomized to placebo (the majority of whom switched to TCZ 8 mg/kg at week 52) showed significantly less PJD versus year 1 (rates for: TSS, 0.1 vs. 0.86; erosion, 0.04 vs. 0.56; JSN, 0.07 vs. 0.31 [p<0.0001 for all three comparisons]).

The rate of progression in radiographic scores for patients randomized to TCZ 4 mg/kg (the majority of whom switched to TCZ 8 mg/kg in year 2), was significantly lower in year 2 versus year 1 for TSS (0.16 vs. 0.25; p = 0.0346) and JSN (0.06 vs. 0.09; p = 0.0138). The rate of progression for the erosion score was lower in year 2 versus year 1, but the difference was not statistically significant (0.09 vs. 0.16; p = 0.1425).

Physical Function

Patients in study WA17823 had mean baseline HAQ-DI scores of 1.5 (all treatment groups). Treatment with TCZ 8 mg/kg + MTX or TCZ 4 mg/kg + MTX resulted in a statistically significantly greater improvement in physical function compared with placebo + MTX at week 52, as assessed by the mean HAQ-DI AUC. This improvement and significant difference between treatment groups were maintained at week 104, even after most patients had switched to open label treatment with TCZ 8 mg/kg. These results were confirmed in sensitivity analyses that included post-escape data.

Table 5 **Analysis of Variance of the AUC of the Change from Baseline in HAQ-DI Score up to Week 52 and up to Week 104 (ITT Population)**

	Placebo + MTX (N=393)	TCZ 4mg/kg + MTX (N=399)	TCZ 8mg/kg + MTX (N=398)
Week 52			
n	366	376	374
Adjusted Mean	-58.11	-128.37	-144.06
Difference		-70.26	-85.95
97.5% CI for difference		(-96.96, -43.56)	(-112.69, -59.22)
p-value		<0.0001	<0.0001
Week 104			
n	366	376	374
Adjusted Mean	-139.40	-287.50	-320.80
Difference		-148.10	-181.40
97.5% CI for difference		(-205.22, -90.98)	(-238.60, -124.21)
p-value		<0.0001	<0.0001

All comparisons were to Placebo + MTX. Analysis adjusted for region. Since physical function was tested at both 52 and 104 weeks, the nominal overall significance level at each time point was set to 0.025. No imputation used for missing HAQ scores. All assessments were set to missing from the
time a patient receives escape therapy, prior to the calculation of the AUC. Where the last observed HAQ score was prior to Week 52 (104), the AUC was standardized to 52 (104) weeks.
Source: $PROD/cdl1935t/jl7823e/reports/etanvarauchaqwk52i.rp8 07MAY2008 16:37;
$PROD/cdl1935t/jl7823f/reports/etanvarauchaqwkl04i.rp8 16APR2009 1:06 PDRD

The results for the primary endpoint are supported by the analysis of the secondary endpoint of a HAQ-DI change from baseline of ≥ 0.3, which showed clinically and statistically significantly higher proportions of patients in the TCZ 8 mg/kg + MTX group (71%) compared with the placebo group (62%) achieving this clinically relevant improvement in HAQ-DI at week 52. The proportion of patients achieving the greatest degree of improvement of ≥0.75 was also higher in the TCZ 8 mg/kg + MTX

group (37%) compared with the placebo + MTX group (28.1%). Improvements in all categories were also observed in the TCZ 4 mg/kg + MTX group, although the difference was not statistically significant when compared with placebo + MTX. These improvements were maintained at week 104.

Improvement in physical function over time

Patients randomized to TCZ + MTX showed a faster improvement in HAQ-DI in the first year compared to the patients randomized to placebo + MTX. The increased rate of improvement in the control group after week 16 may be explained by the fact that 50% of the control patients switched to escape therapy. In the second year of the study, when the majority of patients received open-label TCZ 8 mg/kg + MTX, patients in the placebo + MTX group had a further decrease in HAQ-DI, but the mean remained at a higher level compared with patients treated with TCZ. While the mean HAQ-DI score for patients initially randomized to TCZ 4 and 8 mg/kg + MTX continued to decrease in year 2, the magnitude of decrease in mean HAQ-DI score for patients randomized to TCZ 4 mg/kg + MTX was greater as patients switched to open-label treatment with TCZ 8 mg/kg during this period.

The improvement in physical function as shown in HAQ-DI scores was supported by the results for other patient-reported outcomes, including improvements in physical function scores for the functional assessment of chronic illness therapy (FACIT) fatigue scale and the SF-36. At year 1, significant differences between the TCZ 8 mg/kg and placebo groups were obtained with both SF-36 physical component score and FACIT fatigue scores ($p < 0.05$), and these effects were maintained up to year 2. In the comparison for the TCZ 4-mg/kg group, $p < 0.05$; however, this occurred after the break in hierarchical ordered testing sequence.

Maintenance of HAQ-DI Improvements

The proportion of patients at weeks 52 and 104 who maintained a HAQ-DI improvement of ≥ 0.30 for up to 24, 36, and 48 weeks was greater for patients randomized to TCZ 4 mg/kg or 8 mg/kg than for those randomized to placebo when escape data were set to missing, and when escape data were included. The percentage of patients who had a HAQ-DI of 0 at week 104 (excluding escape data) was higher for patients randomized to TCZ 4 mg/kg (15.0%) and TCZ 8 mg/kg (15.4%) than for patients who were randomized to placebo (10.9%). A similar trend was observed when escape data were included.

The data from study WA17823 are supported by the results of an exploratory analysis of pooled data from the extension phase of study WA17823 and the open label extension studies WA18695 and WA18696. In this analysis, HAQ-DI scores were re-base lined after 24 weeks of TCZ treatment to assess whether there was further improvement following the initial large improvement in HAQ-DI observed after 24 weeks. Further improvement was seen, however the effect was small (- 0.046, 95% CI [-0.056, -0.037]). These results demonstrate that the effect on physical function status after week 24 in patients treated with TCZ 8 mg/kg was not only maintained but continued to improve throughout the 3 year observation period.

Reductions in HAQ-DI scores were demonstrated in both an aggregate trends model and in a mixed effects model.

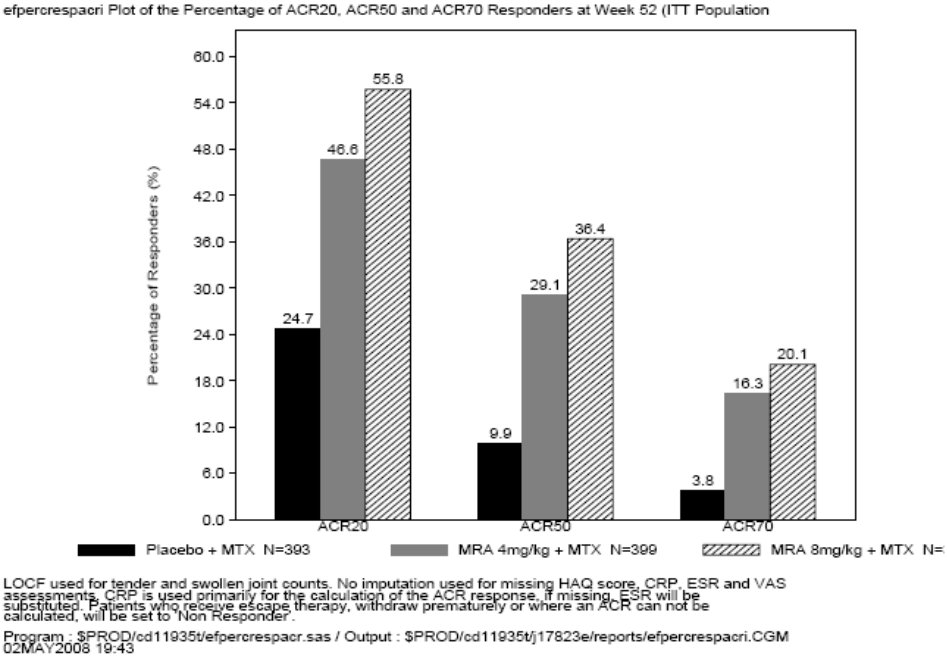
Reduction of signs and symptoms

ACR20, ACR50, and ACR70 Responses

The proportion of patients achieving ACR20, ACR50, and ACR70 responses in the TCZ 4- and 8-mg/kg groups at week 52 was significantly greater than that in the placebo group ($p < 0.0001$ for all

comparisons. Between the two TCZ groups, numerically greater response rates were seen with the 8- as compared with the 4-mg/kg dose.

Figure 5 **Percentage of ACR20, ACR50, and ACR70 Responders at Week 52 (ITT Population)**



The ACR20/50/70 response rates (excluding escape data and including escape data) achieved in year 1 were maintained throughout year 2. Following initiation of open-label TCZ 8-mg/kg treatment at week 52, the placebo and 4-mg/kg groups showed a rapid increase to response levels similar to those seen for patients in the 8-mg/kg group. For patients receiving TCZ 8 mg/kg, ACR50 and ACR70 response rates increased between week 52 and week 104 (from 36% to 39% and from 20% to 22%, respectively).

DAS28 Response

• Patients receiving TCZ treatment on average showed continuous improvement in DAS28 scores over 2 years; the greatest improvements in DAS28 response were observed with the TCZ 8 mg/kg dose

• The proportion of patients achieving DAS28 remission increased continuously over 2 years treatment with TCZ

• Patients who switched from control or TCZ 4 mg/kg to TCZ 8 mg/kg at week 52 showed considerable improvement in DAS28 scores at week 104

At week 52, both TCZ-treated groups showed a significantly greater decrease in DAS28 compared with the control group ($p < 0.001$ for both comparisons); the greatest mean change from baseline in DAS28 was observed in the TCZ 8 mg/kg group. In the TCZ 8-mg/kg group, mean scores approached the DAS28 threshold for clinical remission (< 2.6) at the end of the 52-week treatment period (mean score of 2.77; ITT population, escape data excluded).

In the second year of study WA17823 when the majority of patients received open label TCZ 8 mg/kg, mean DAS28 scores continued to decrease for all treatment groups. At week 104, mean DAS scores for both the placebo and 4-mg/kg groups approached the DAS28 threshold for clinical remission (2.75 and 2.81, respectively), while the 8-mg/kg group attained the lowest mean DAS28 score, 2.55 (escape data included). Results of the sensitivity analyses for mean DAS28 score and DAS28 mean change

from baseline (including escape data and excluding escape data) were similar to those of the primary analysis.

At week 104, both proportions of patients in DAS28 remission and those achieving low disease activity showed a further increase from year 1. The TCZ 8 mg/kg + MTX group continued to show the greatest proportion of patients achieving these targets, with nearly two-thirds of high-dose patients achieving DAS28 remission and 76% showing low disease activity. The sensitivity analysis for DAS28 remission/disease activity showed similar improvements for year 2.

EULAR Response

Consistent with the results for DAS28, the proportion of patients achieving a moderate or good EULAR response was greater in the TCZ groups than in the placebo group at week 52. The percentage of patients who achieved a good or moderate EULAR response increased further in year 2 for patients randomized to placebo or TCZ 4 mg/kg, and was maintained for patients randomized to TCZ 8 mg/kg, with half of the patients in this group achieving a EULAR good response.

Dose Recommendation

Based on the results of the 6-month controlled trials in the marketing authorisation application, the dose of TCZ 8 mg/kg was recommended for treatment of signs and symptoms. TCZ 8 mg/kg + MTX has been shown to be effective regarding the prevention of joint damage and improvement in physical function as assessed in study WA17823, and supported by the maintenance of efficacy for the long-term data in the open-label extension studies.

Study WA17823 was not formally designed to compare results for the two TCZ doses; however, the results support previous findings, which showed numerically better responses for patients receiving TCZ 8 mg/kg as compared with 4 mg/kg. Radiographic data indicated a greater inhibition of radiographic progression over 2 years for patients randomized to TCZ 8 mg/kg as compared with those who started the study on 4 mg/kg. The higher dose showed a 74% inhibition of radiographic progression at week 52, which increased to 81% at week 104. The 4- mg/kg group showed an inhibition of 70% at both time points.

Similarly, the increase from year 1 to year 2 in the proportion of patients without progression of joint damage (TSS ≤ 0) was greater for the TCZ 8-mg/kg group (83% in year 1 versus 93% in year 2) as compared with the 4-mg/gkg group (78% versus 81%). Moreover, annualized progression rates for TSS showed a further decrease in progression of joint damage after patients switched from TCZ 4 mg/kg to 8 mg/kg (-68% in annualized progression rate before the switch).

The TCZ 8-mg/kg group showed a greater magnitude of improvement in HAQ-DI at week 52 compared with the control group (translating into a statistically greater proportion of patients with an improvement of 0.3 [63%; p = 0.0389]). HAQ-DI scores for TCZ 4 mg/kg differed numerically from those of control (60%; p = 0.1909). A greater proportion of TCZ 8 mg/kg patients achieved ACR20/50/70 responses and DAS28 clinical remission compared with patients receiving 4 mg/kg.

Persistence of Efficacy

Long-term efficacy data were obtained in a total of 4009 patients for up to 192 weeks, including over 1000 patients treated for 156 weeks (3 years). Maintenance of the clinical benefit of TCZ for up to 192 weeks was assessed using pooled data (All Exposure population) from the core studies and the ongoing, open-label extension studies (WA18695 and WA18696 and patients in WA17823 continuing in the long term extension portion of that trial). In these studies, baseline was defined as the first active dose of TCZ (either in the core or the extension study). Key efficacy data are provided from the time patients received their first dose of TCZ up to the cut off date of February 6, 2009.

Patients Withdrawn from Treatment

As of the data cut-off point (February 6, 2009), 1064 patients (26.5%) had withdrawn from treatment. A small proportion of these were patients discontinued due to insufficient therapeutic response (152/4009, 3.8%).

The WA18062 (anti-TNF non-responders) group had the greatest proportion of withdrawals due to insufficient therapeutic response (2.4%, 10.6%, and 2.9% for the WA17824, WA18062, and Pooled groups, respectively).

All patients received TCZ 8 mg/kg on entering the extension studies. Efficacy was assessed every 12 weeks (every 8 weeks in WA17823) and summarized in three study groups within the All Exposure population, according to the type of patient population treated in the core study:

1) the Pooled group (consisting of patients with inadequate response to MTX/DMARDs randomized into WA17822, WA17823, or WA18063);

2) the WA17824 (monotherapy) group;

3) the WA18062 (anti-TNF inadequate responders) group.

Efficacy was either maintained or continued to improve with duration of treatment in patients who received TCZ, as demonstrated by continued improvements in ACR responses and DAS28 and EULAR scores (no radiographic assessments were performed). Most notable was the incremental benefit provided over time, as demonstrated by increasing proportions of patients achieving the higher response levels for efficacy. In addition, patients who were initially randomized to TCZ 4 mg/kg in the core study showed further improvement after switching to 8 mg/kg therapy in the extension studies. These patterns of improvement were evident in all study populations. Patients in the WA17824 group (who started on monotherapy treatment and could remain on it during the extension phase) consistently showed the best responses for all parameters, reflecting their earlier stage of disease and history of fewer failed DMARDs. Those in the WA18062 (anti-TNF non-responders) group generally had relatively lower responses, reflecting the later stage and refractory nature of their disease. These patients nevertheless showed considerable improvement over time.

The majority of patients in the extension studies were receiving concomitant background DMARD therapy. However, in core study WA17824 and its extension study WA18695, patients received TCZ as monotherapy (patients were permitted to add background DMARDs in the extension phase). In the All Exposure Population, the WA17824 group consisted of all patients who received TCZ, including those who were randomized to MTX and later switched to open label TCZ 8 mg/kg. An analysis of a subgroup of 234 patients who received only TCZ 8 mg/kg as monotherapy throughout the core (WA17824) and extension study (up to the data cut) also demonstrated maintenance of, or further improvement in, ACR response rates and DAS28/EULAR scores.

Patients Who Experienced Loss of Efficacy

A total of 152 patients in the All Exposure population withdrew for insufficient therapeutic response. Of these, 66 (43.4%) were positive for neutralizing antibodies at any time, including baseline. Anti-drug antibodies have been associated with a loss of clinical efficacy in patients treated with biological therapies. Approximately one third of patients (14 of 34 tested; 35 total) who had an ACR50 or DAS28 EULAR good response prior to withdrawing due to a lack of efficacy had a positive neutralizing antibody test post baseline.

A total of 127 patients (3.2% of total population) had tested positive for neutralizing antibodies; of these, 66 (52.0% of neutralizing antibody-positive population) withdrew for lack of efficacy and 14

(11.0% of neutralizing antibody-positive population and 0.36% of the 3937 patients tested) achieved good efficacy but subsequently lost it.

Discussion on clinical efficacy

The results of Study WA17823, obtained by the interim analysis at Week 24, have already been evaluated during the previous submission. There were no objections on this data.

The two co-primary endpoints have been met and consistent results are demonstrated compared to the MAA. Inhibition of structural damage and improvement of physical function at week 52 is demonstrated. Efficacy is maintained as assessed by ACR20, DAS28 and EULAR response data. ACR50 and ACR70 assessment at week 52 indicate a sufficient response rate, expectedly on a lower fraction of patients. This analysis shows that response is continually maintained in a considerable fraction of patients until the week 52 assessment.

Both of the co-primary endpoints were met at week 104. Treatment with TCZ 4 mg/kg and 8 mg/kg + MTX reduced the rate of progression of joint damage compared with placebo + MTX. A greater proportion of patients in the TCZ 8 mg/kg group had no progression of joint damage at the end of year 2 compared with patients randomized to placebo. Results for all radiographic endpoints at week 104 showed maintenance of effect with regard the benefits obtained in the first year of the study.

The examination of radiographic endpoints at week 52 and week 104 of the study showed sustained inhibition of structural damage with the highest protective level in the TCZ 8mg/kg dose group. Including data from withdrawal and post-escape patients instead of using linear extrapolation leads to an expected flattening of the mean change plot in the placebo population.

The examination of the endpoint measuring improvement of physical function at week 52 and week 104 of the study showed sustained improvement and maintenance of 3 years with the highest improvement level in the TCZ 8mg/kg dose group. The presented data does support the proposed SmPC wording.

The presented data shows maintenance of reduction of signs and symptoms of RA during year one and two of the long term studies. Sustained efficacy could be assessed with all used instruments of measuring efficacy as ACR, DAS28 and EULAR response. Although the data is not subject of the current variation it is still seen as supportive and positive.

The number of patients developing human anti-human antibodies (HAHA) is considered low and not increasing over treatment time. Even though numbers are very small a trend is notable that patients developing neutralising antibodies experience a loss of efficacy and tend to withdraw from the study. So the judgement from the initial data from MAA that efficacy was not impaired in patients with neutralizing HAHA, is not fully acceptable any more. As the percentage of patients developing antibodies is still low, no further consequences need to be taken but data regarding antibody development need to be kept in focus.

3.3.3 Clinical safety

Patient exposure

All Exposure Population: this is the primary population for assessment of the long-term safety and tolerability of TCZ and includes patients from studies WA17822, WA17823, WA17824, WA18062, WA18063 and WP18663 who received at least one dose of TCZ, regardless of whether or not they entered long-term extension studies WA18695 or WA18696 or continued into the extension phase of study WA17823. This analysis pools data from the core studies (including the transition phase of study WA17824), and the WA17823, WA18695 and WA18696 extension studies where applicable (i.e., if the

patient has such data available). Up to the cut-off date, the 4009 patients included in this population provide a total of 8580 patients-years exposure to TCZ. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 received treatment for at least 1 year, 2806 received treatment for at least 2 years, and 1222 received treatment for at least 3 years.

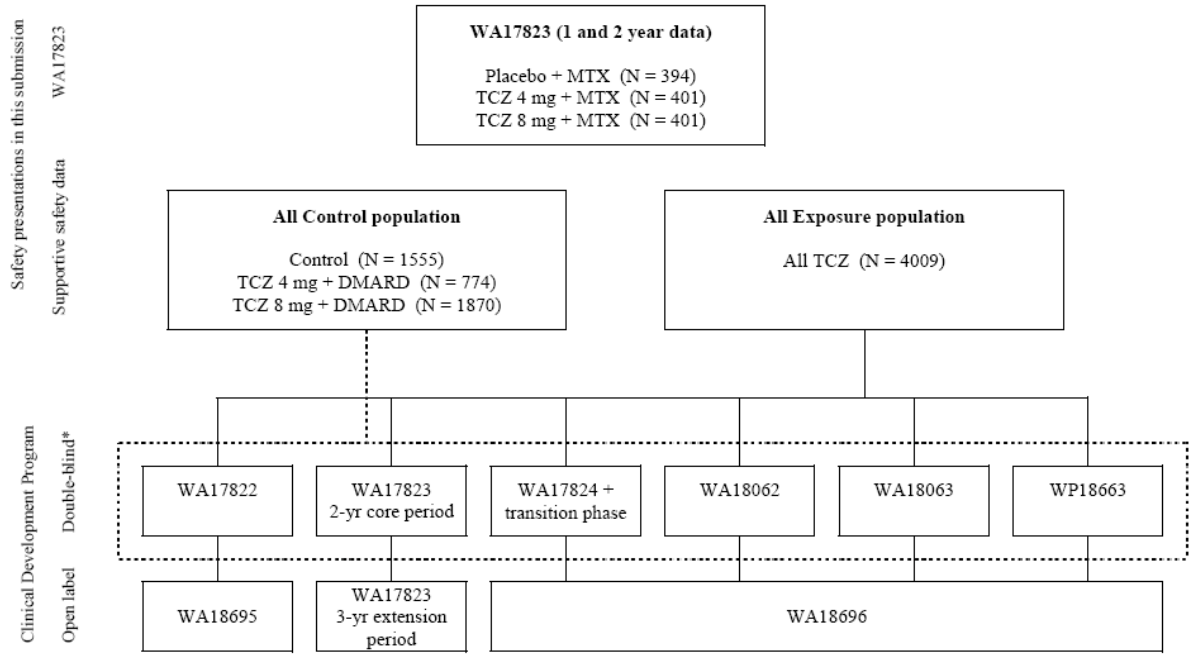
All Control Population: additional safety analyses were performed on this population to elucidate the effect of TCZ dose level on specific AEs and laboratory abnormalities of interest. The All Control population includes all patients randomized to one of the five core Phase III studies (WA17822, WA17823 [2-year core period], WA17824 [including the transition phase], WA18062 and WA18063). Only data from the double-blind phases of each core study are included and data from the point that a patient changes treatment regimen are excluded. Change in treatment regimen includes: entering escape therapy, changing TCZ dose, changing to open label TCZ. Safety data from study WP18663 are excluded.

Under controlled conditions in the Phase III studies, 1555 patients received control treatment, 774 patients received TCZ 4 mg/kg and 1870 patients received TCZ 8 mg/kg. Post-marketing safety information is also provided up to a cut-off date of April 11, 2009

In the first year of study WA17823, the total patient-years of duration on trial treatment, defined as the time from initial dose of study medication to the time of treatment switch for patients who increased their TCZ dose or to the time of the last safety observation for patients who did not change dose, was 256.13 year in the placebo + MTX group, 328.71 years in the TCZ 4 mg/kg + MTX group, and 349.15 year in the TCZ 8 mg/kg + MTX group. The additional year of treatment in the second year of the study primarily increased exposure to the TCZ 8 mg/kg dose reflecting both the high proportion of patients whose only dose of TCZ was 8 mg/kg and the high proportion of patients who switched from the other regimens. Thus, by week 104, the highest total patient-years of treatment duration was in the pool of all patients treated with TCZ 8 mg/kg (1320.4 years). Patients whose only dose of TCZ was 4 mg/kg had the lowest total duration of treatment by week 104 (183.3 years), reflecting the high proportion of patients who switched to the higher dose.

Considering cumulative exposure in the RA clinical trial program, 4,009 patients have received at least one dose of TCZ as of the clinical cut-off date (February 6, 2009), providing a total of 8579.7 patient-years of exposure and 9414.3 patient-years of observation. Overall this represents a 3-fold increase in exposure to TCZ since the original application.

Figure 6 **Overview of the Clinical Program and Safety Presentations Included in this Submission**



*Double-blind except for open label clinical pharmacology study WP18663. In study WA17823, the majority of patients received open label treatment with TCZ 8 mg/kg during year 2 (s

Study WA17823 Safety Analysis Approach

For the year 1 analysis, safety data were presented according to initially randomized treatment. Safety data obtained after initiation of escape therapy were censored and provided separately. Consequently, this analysis enables a between-group comparison and thus establishes the safety profile of TCZ 4 mg/kg and 8 mg/kg in comparison with control. However, as patients were expected (per the study design) to switch to open label treatment with TCZ 8 mg/kg in the second year, such an analysis approach for the cumulative analysis up to week 104 would have censored the majority of the year 2 data, resulting in a minimal increase in exposure and safety data.

The analysis at week 104 thus assessed patients on the basis of the treatment received rather than the treatment to which they were originally randomized, an approach which allowed inclusion of not only the new safety data accrued in year 2 but also post-escape safety data from year 1 into the main analysis. As a consequence, the utility of between-group comparisons from the cumulative data up to week 104 is limited and the main focus of the dataset is on the assessment of long-term safety and the safety profile in patients who switched treatment regimens.

Two complementary presentation approaches were employed for the cumulative safety data up to week 104, namely by treatment–switch groups and by pooling all data on a particular regimen (e.g., all data from patients receiving TCZ 4 mg/kg including those originally randomized to this dose and those randomized to placebo who entered escape therapy).

Withdrawals – WA17823

Of the 1190 randomized patients who received study treatment, a total of 281 withdrew prematurely from the study up to week 104. As described in the 1-year CSR, 170 patients withdrew during the first 52 weeks of the study: 128 patients from initial randomized treatment (36 in the placebo + MTX group, 44 in the TCZ 4 mg/kg + MTX group and 48 in TCZ 8 mg/kg + MTX group), 37 patients from escape 1 therapy (21 on TCZ 4 mg/kg + MTX and 16 on TCZ 8 mg/kg + MTX) and five (5) patients

from escape 2 therapy. Overall, more patients withdrew for safety-related reasons, namely AEs or intercurrent illness, while receiving TCZ treatment than while receiving placebo treatment. In the cumulative data up to week 104, premature withdrawals for any reason are disproportionately represented in the group of patients whose only dose of TCZ was 4 mg/kg as the study was designed to switch those patients remaining in the study to open label TCZ 8 mg/kg after week 52. Conversely, the group of patients who switched from TCZ 4 mg/kg to 8 mg/kg had a lower rate of such events since, by definition, they did not discontinue on the 4 mg/kg dose.

Withdrawals – Pooled Long-Term Data

One thousand and sixty-four patients (1064) (27%) withdrew from the All Exposure population after at least one dose of TCZ treatment note, this includes the withdrawals from the TCZ + MTX groups in study WA17823 described above). Withdrawals due to safety and non-safety reasons occurred in a similar proportion of patients (14% and 13%, respectively). Five-hundred and eight patients (508) (12.7%) prematurely withdrew due to AEs/laboratory abnormalities. A total of 50 deaths were reported in the All Exposure population. The most common non-safety reasons for early withdrawal were "refusal of treatment" (223 patients, 5.6%), and "insufficient therapeutic response" (152 patients, 3.8%). Other non-safety reasons for early withdrawal were "other" (74 patients, 1.8%), "failed to return" (58 patients, 1.4%), "other protocol violation" (6 patients), and "violation of selection criteria at entry" (4 patients).

Adverse events

In all studies, safety monitoring included the collection of information on adverse events (AEs), deaths, serious adverse events (SAEs), reasons for withdrawals, laboratory tests, vital signs and electrocardiograms (ECGs).

WA17823 1-year Analysis

During initial randomized treatment up to week 52, the proportion of patients with at least one AE was higher in each of the TCZ + MTX groups compared with the placebo + MTX group, the difference being mainly attributed to higher percentages of patients in the TCZ + MTX groups who experienced AEs in particular system organ classes (SOCs) including infections and infestations, GI disorders, skin and subcutaneous tissue disorders, and investigations (most of which were related to events of liver function test abnormalities). Differences between the groups in extent of exposure to initial randomized treatment should also be taken into account when examining the prevalence of AEs across the treatment groups. SAEs, AEs leading to withdrawal and AEs leading to dose modification all occurred in a higher proportion of patients in the TCZ + MTX groups than in the placebo + MTX group. Six patients died, one in the placebo + MTX group, one in the TCZ 4 mg/kg + MTX (escape 1 therapy) group and four in the TCZ 8 mg/kg + MTX group (one of whom was on TCZ 8 mg/kg to 8 mg/kg escape 1 therapy).

WA17823 2-year Analysis

In the analysis according to originally randomized treatment group, between-group differences identified during year 1 were retained, although direct comparison between groups in the cumulative data to week 104, particularly with placebo, is confounded by the fact that the additional data in this analysis were accrued primarily with TCZ 8 mg/kg in year 2. The placebo data thus remain unchanged from year 1. The nature and frequency of AEs (including deaths, SAEs, and AEs leading to treatment withdrawal or dose modification) remained consistent with the profile documented in year 1, as shown by analyses of the cumulative data up to week 104 both by treatment switch-groups and by each regimen pooled.

Most of the additional safety data in year 2 was accrued in patients whose only dose of TCZ was 8 mg/kg (i.e., patients initially randomized to this dose or who switched to open label treatment in year 2). Comparison of this group with data obtained for the same dose group up to week 52 showed that the safety profile established in year 1 remained unchanged with increasing exposure to TCZ 8 mg/kg in year 2.

The second largest incremental set of data in year 2 was post-switch data obtained in patients who increased their TCZ dose from 4 mg/kg to 8 mg/kg. In this subset of patients, the incidence of AEs and laboratory data abnormalities that have been shown to be TCZ dose-dependent increased after the switch to TCZ 8 mg/kg to more closely resemble rates observed for the higher dose.

In the All Control population, a dose-dependent increase in the overall rate of AEs was observed in the TCZ 8 mg/kg group (381.6 per 100 patients-years) compared with the TCZ 4 mg/kg group (358.0 per 100 patient-years).

In the All Control population, infections were the most frequently reported type of AEs. Marked differences were observed between the TCZ treatment groups and control treatment group in the rate of AEs for the following SOCs: Skin and subcutaneous disorders, primarily driven by events of rash and pruritus; Investigations; primarily driven by events of increased transaminases including transaminases increased, ALT increased, hepatic enzyme increased, liver function test abnormal, AST increased, and ALT abnormal; Neoplasms, primarily driven by multiple events of single occurrence

Minor differences were observed between the TCZ treatment groups and control treatment group in the rate of AEs for the following SOCs: Infections and infestations, predominantly driven by events of upper respiratory tract infections; Vascular system disorders, primarily driven by hypertension; Eye disorders, primarily driven by events conjunctivitis; Blood and lymphatic system disorders, primarily driven by events of neutropenia/leukopenia; Endocrine disorders, primarily driven by events of thyroid dysfunction

Nervous system disorders, metabolism and nutrition disorders, renal and urinary disorders, and hepatobiliary disorders occurred at similar rates across the three treatment groups, however, the following events were reported more frequently in TCZ-treated patients compared with control-treated patients: Headache; Dizziness; Hypercholesterolemia; Nephrolithiasis; Hepatic steatosis

In the All Exposure population, the overall rate of AEs was 332.2 per 100 patient-years, which is similar to the rate reported previously.

The rate of AEs was highest in the first 6 months of treatment with TCZ and decreased thereafter.

Adverse Events Considered to be related to Study Drug by the Investigator

WA17823

During initial randomized treatment up to week 52, AEs considered by the investigator to be related to treatment were reported by more patients in the TCZ + MTX groups (4 mg/kg, 50%; 8 mg/kg, 55%) than in the placebo + MTX group (40%), this difference being mainly attributed to greater numbers of patients who experienced GI disorders or abnormal investigations (mostly elevations in hepatic enzymes) considered by the investigator to be related to TCZ + MTX treatment. A higher percentage of patients in the TCZ + MTX groups (4 mg/kg, 3% and 8 mg/kg, 4%) experienced SAEs (mostly serious infections and infestations) considered by the investigator to be related to trial treatment compared with patients in the placebo + MTX group (2%).

In the cumulative data up to week 104, there was no increase in the rate of AEs considered by the investigator to be related to trial treatment either with prolonged exposure to TCZ 8 mg/kg or among

patients who increased their TCZ dose from 4 mg/kg to 8 mg/kg. The types of AEs considered by the investigator to be related to trial treatment were consistent with those described up to week 52.

Pooled Controlled and Long-Term Data

In the All Exposure population, the rate of AEs considered by the investigator to be related to treatment was 112.8 per 100 patient-years. There was no evidence of an increased risk of a patient experiencing a treatment-related AE with continued exposure to TCZ.

Serious adverse events and deaths

SAEs

Serious Adverse Events – WA17823

During initial randomized treatment up to week 52, a higher proportion of patients in the TCZ + MTX groups experienced SAEs compared with the placebo + MTX group. SAEs occurred most frequently in the following SOCs: infections (mainly pneumonia), injury and poisoning (primarily fractures of various types), neoplasms, GI disorders, nervous system disorders and cardiac disorders. Infections and infestations, the most frequently reported SAEs, were observed in 2.5% of patients in the TCZ 4 mg/kg + MTX group, 3.0% of patients in the TCZ 8 mg/kg + MTX group and 1.5% of patients in the placebo + MTX group. Neoplasms were more frequent in the TCZ 4 mg/kg + MTX group (2.5%) than in the TCZ 8 mg/kg + MTX group (0.3%).

SAE rates in patients on escape therapy were similar to those observed in patients during initial randomized treatment.

In the cumulative data up to week 104, the overall profile of SAEs was comparable to that reported up to week 52, with no changes in either the nature or the rates per 100 patient-years with prolonged exposure to TCZ 8 mg/kg. For patients who increased their dose of TCZ from 4 mg/kg to 8 mg/kg, the rate of SAEs increased after the treatment switch to a rate comparable with that for patients whose only dose of TCZ was 8 mg/kg (11.4 per 100 patient-years).

Serious Adverse Events – Pooled Controlled and Long-Term Data

In the All Control population, the rate of SAEs was similar across the three treatment groups (control, 14.4 per 100 patient-years; TCZ 4 mg/kg, 13.6 per 100 patient-years; TCZ 8 mg/kg, 14.5 per 100 patient-years). The most frequently reported type of SAEs were infections and infestations which occurred at a higher rate in the TCZ 8 mg/kg group (4.8 per 100 patient-years) compared with the TCZ 4 mg/kg and control treatment groups (3.5 and 3.3 per 100 patient-years, respectively). The frequency of SAEs in other SOCs was comparable between patients treated with TCZ and patients who received control treatment.

In the All Exposure population, the rate of SAEs was 14.9 per 100 patient-years, which is similar to the rate reported previously. There was no evidence of an increased risk of SAEs with prolonged exposure to TCZ, as demonstrated by the similar rates of SAEs per 100 patient-years by 6 monthly intervals of exposure.

The most frequently reported type of SAEs was infections and infestations (4.4 per 100 patient-years), of which pneumonia (0.8 per 100 patient-years) and cellulitis (0.5 per 100 patient-years) were the most common. The second most frequently reported type of SAEs was injury, poisoning, and procedural complications (1.3 per 100 patient-years), with various types of fractures contributing to the majority of the events reported in this SOC.

When comparing the rates of SAEs by SOC and the rates of individual events that led to treatment withdrawal, only a fraction of SAEs led to patient withdrawal, except for malignancies and individual events that led to death (primarily fatal infections and cardiac events).

Analysis of Adverse Events Leading to Withdrawal – WA17823

During initial randomized treatment up to week 52, 7.3% and 8.5% of patients in the TCZ + MTX groups (4 mg/kg and 8 mg/kg, respectively), experienced AEs and laboratory abnormalities that led to premature withdrawal compared with 2.6% of patients in the placebo + MTX group. Elevations in hepatic enzymes(i.e., increased transaminases, increased ALT, increased bilirubin, increased hepatic enzymes), the most common AE leading to withdrawal, were more frequent in the TCZ + MTX groups (4 mg/kg + MTX, 1.8% and 8 mg/kg + MTX, 4.5%) compared with the placebo + MTX group (0.3%); this reflected per-protocol requirements to withdraw patients with either ALT/AST values > 5x ULN, indirect bilirubin > 2x ULN, or total bilirubin > 43 µmol/L. Serious infections led to premature withdrawal in four (4) patients (1%) in each of the TCZ + MTX dose groups and one patient (0.3%) in the placebo + MTX group. Six patients (1.5%), all in the TCZ 4 mg/kg + MTX group, withdrew prematurely due to neoplasms. The remaining AEs leading to withdrawal were individual AEs in different SOCs. Among patients who experienced AEs that led to premature withdrawal, 64% in the TCZ 4 mg/kg + MTX group and 69% in the TCZ 8 mg/kg + MTX group did so within the first 6 months, compared with 56% in the placebo + MTX group. During escape therapy up to week 52, a total of 13 patients (2.1% to 5.5%) experienced AEs that led to premature trial treatment withdrawal, the most common of which were anaphylactic shock/reaction (3 patients) and drug hypersensitivity (1 patient) in the MTX to TCZ 4 mg/kg + MTX escape group. In the cumulative data up to week 104, the overall profile of AEs leading to premature trial treatment withdrawal was comparable to that reported up to week 52, with no changes in either the nature or the rates per 100 patient-years with prolonged exposure to TCZ 8 mg/kg. By definition, patients who switched from TCZ 4 mg/kg to TCZ 8 mg/kg did not withdraw prematurely from the lower dose. After the switch to TCZ 8 mg/kg, the rate of AEs leading to withdrawal (7.4 per 100 patient-years) was consistent with that for patients whose only dose of TCZ was 8 mg/kg (7.3 per 100 patient-years).

Analysis of Adverse Events Leading to Withdrawal – Pooled Controlled and Long-Term Data

In the All Control population, the rate of AEs leading to withdrawal was 6.9 per 100 patient-years in the control group compared with 10.1 and 10.2 per 100 patient-years in the TCZ 4 mg/kg and TCZ 8 mg/kg groups, respectively. The types of events leading to withdrawal differed in the three treatment groups, with infections being the most common in the control group and investigation AEs, primarily liver function test abnormalities, being the most common in the TCZ treatment groups. In the All Exposure population, the rate of AEs leading to withdrawal was 5.8 per 100 patient-years. The overall rate of AEs leading to withdrawal was highest (11.5 per 100 patient-years) during the first 6 months of treatment and steadily decreased thereafter. The majority of events resolved after withdrawal of the patient.

The most frequently reported types of AEs leading to withdrawal were investigations (1.3 per 100 patient-years, primarily due to events of liver function test abnormalities), infections and infestations (1.1 per 100 patient-years), and neoplasms (benign, malignant, or unspecified; 0.7 per 100 patient-years).

Infection Adverse Events

In the All Control population, the overall rate of infections was 95.9 per 100 patient years for the control group, 101.8 per 100 patient-years for the TCZ 4 mg/kg group, and 102.3 per 100 patient-years for the TCZ 8 mg/kg group. Upper respiratory tract infections (e.g., upper respiratory tract

infections, nasopharyngitis, bronchitis, influenza, and sinusitis) and urinary tract infections were most commonly reported.

The overall rate of infections reported in the All Exposure population was 108.0 per 100 patient-years of exposure. The rate of infections was highest in the first 6 months and decreased thereafter. The overall profile of infections was consistent with data reported previously with upper respiratory tract (e.g., upper respiratory tract infections, nasopharyngitis, and bronchitis) and urinary tract infections being most commonly reported.

Serious Infections

In the All Control population, the overall rate of serious infections was 3.4 per 100 patient-years for the control group, 3.5 per 100 patient-years for the TCZ 4 mg/kg group, and 4.9 per 100 patient-years for the TCZ 8 mg/kg group. The events most commonly reported were pneumonia, cellulitis, urinary tract infection, and gastroenteritis. In the All Exposure population, the rate of serious infections was 4.66 per 100 patient-years, which is similar to the rate of serious infections reported previously and to that reported in the literature for other biologics.

The most commonly observed serious infections in patients treated with TCZ were pneumonia and skin and soft tissue infections.

Opportunistic Infections

In the All Exposure population, a total of 22 opportunistic infections were reported in 20 patients. The current rate of opportunistic infections is 0.2 per 100 patient-years. Fourteen (14) of the 22 opportunistic infections were serious. Of the 22 opportunistic infections, two (9%) led to a fatal outcome, nine (41%) (including the two deaths) led to discontinuation from treatment with TCZ, and five (23%) led to TCZ dose modification. One patient with systemic candida also had concomitant staphylococcal sepsis which, in the investigator's opinion, was the cause of death.

Cumulatively, nine (9) events of tuberculosis (TB), eight (8) pulmonary and one (1) extra-pulmonary, and one (1) mycobacterium urinary tract infection (acid-alcohol resistant bacillus; BAAR positive) were reported in the All Exposure population.

Deaths

There were a total of nine (9) deaths in TCZ-treated patients up to week 104; four (4) were reported during year 2. All but one patient, who was receiving TCZ 4 mg/kg + MTX, were receiving TCZ 8 mg/kg + MTX. The deaths were due to pulmonary embolism (TCZ 4 mg/kg + MTX), gastroesophageal cancer, metastatic malignant melanoma, metastatic lung adenocarcinoma, cardiomyopathy, cerebral haemorrhage, gastrointestinal infection, bronchopneumonia, and sepsis.

Overall Summary of Deaths – Pooled Controlled and Long-Term Data

In the All Exposure population, a total of 50 deaths have been reported in patients who received at least one dose of TCZ.

The principle causes of death as reported by the investigators include cardiac events (13 cases), serious infections (12 cases), and malignancies (8 cases). Serious infections were ongoing in five (5) patients at the time of death, however, the investigator did not judge the infections as the primary cause of death.

In TCZ-treated patients, the overall rate of death is 0.53 per 100 patient-years of exposure, which is consistent with the previously reported rate. In comparison, the overall rate of death for patients on

control therapy is 0.73 per 100 patient-years (6 deaths in 824.56 patient-years exposure). Of the 50 deaths reported in patients treated with TCZ, one occurred in a patient receiving TCZ 4 mg/kg and 49 occurred in patients receiving TCZ 8 mg/kg (resulting in rates of 0.97 and 0.53 deaths per 100 patient-years, respectively). The overall rate of death due to infection as judged by the investigator is 0.13 per 100 patient-years of exposure, which is also consistent with the rate reported previously.

Laboratory findings

Anti-TCZ antibodies

The development of anti-TCZ antibodies was low, with about 1.0% of patients developing confirmation assay positive specific anti-TCZ antibodies and 3% developing neutralizing antibodies. The majority of patients who developed specific or neutralizing antibodies did so by week 24. The development of anti-TCZ antibodies had no apparent effect on the frequency or type of AEs reported. Only eight (8) of 3937 patients (0.2%) experienced a clinically significant infusion reaction in association with anti-TCZ antibodies. In addition, among patients who missed ≥ 2 consecutive infusions, there did not appear to be significant production of specific or neutralizing anti-TCZ antibodies.

Neutropenia

Clinically significant neutropenia was observed infrequently in patients receiving TCZ and there was no apparent association between decreases in neutrophil counts and the nature or frequency of infections; however, the MAH recommends caution when considering initiation of TCZ treatment in patients with a low neutrophil count and. In patients with an absolute neutrophil count < 0.5 x 109/L, treatment is not recommended. No effects on bone marrow or neutrophil function have been reported with TCZ in animal studies.

Change in transaminase levels

Transient mild and moderate elevations of hepatic transaminases have been observed commonly with TCZ treatment, particularly when TCZ is administered in combination with DMARDs (mainly MTX). Although these elevations have not been treatment limiting in the vast majority of patients and have been observed without progression to hepatic injury, the MAH recommends caution when considering treatment of patients with active hepatic disease or hepatic impairment. Data indicate that treatment can be successfully resumed without recurrence of elevations following decrease of hepatic transaminases.

Change in lipid levels

Initiation of TCZ is associated with elevation of total cholesterol, HDL, LDL and triglycerides. Absence of findings from non-clinical and healthy volunteer studies conducted with TCZ at a range of doses, combined with the observation that lipid parameter elevations have also been reported with other biological RA therapies, provide initial evidence that these elevations may occur as a result of a reduction in chronic inflammation rather than a direct effect of TCZ on lipid metabolism. There was no evidence to suggest that changes in the lipid profile were associated with clinical manifestations such as cardiovascular adverse events. There were also profound reductions in CRP, high levels of which represent a major risk factor for cardiovascular morbidity. In the small number of patients who had an adverse change in lipid profile, based on lipid elevations alone, initiation of treatment with a statin was effective.

Safety in special populations

Subpopulation analyses of the five core Phase III studies at 24 weeks did not identify any notable differences across demographic subgroups defined by age, gender, region, race, weight and BMI, and renal function (mild renal impairment).

Further exploration of safety in subpopulations was performed for certain parameters at 1 year in study WA17823 and, for infection AEs in particular, in the pooled controlled and long-term safety populations.

In summary, serious infections occurred at a higher rate in the following subpopulations of TCZ-treated patients: patients > 65 years of age, patients in the higher weight and highest and lowest BMI categories, patients with prior co-morbidities that predispose them to infections (diabetes, chronic pulmonary disease), patients who previously received anti-TNFs and patients taking background corticosteroids; the highest rates were generally observed in the TCZ 8 mg/kg group.

Control-treated patients showed similar trends for increases in serious infections by age, BMI, prior co-morbidities and prior anti-TNF use.

Discussion on clinical safety

The data suggest that there are no additional significant safety issues after extended treatment with RoActemra and risk minimisation strategies exist and are detailed within the risk management plan, product information and within clinical guidelines.

Patients showed a higher rate of treatment related SAE, AE leading to withdrawal and AE leading to dose interruption on the 8 mg/kg + MTX dosing schedule compared to the 4 mg/kg + MTX dosing schedule. Patients on escape therapy portrayed similar range and intensity of side effects as the TCZ + MTX 8mg/kg group.

The terms "Urticaria" and "Peripheral oedema" are integrated in the tabular overview of AEs in the SPC to reflect the above described findings. The terms "Nephrolithiasis" and "Hypothyroidism" are integrated as uncommon AEs in the tabular overview of AEs in the SPC to reflect the above described findings.

Most of the safety data in year 2 was accrued in patients whose only dose of TCZ was 8 mg/kg (i.e., patients initially randomized to this dose or who switched to open label treatment in year 2). The safety profile of study year 1 does not change significantly with increasing exposure to TCZ 8 mg/kg in year 2.

Overall the presented data shows that the safety profile or RoActemra remains relatively stable over longer treatment periods and that the highest incidence of adverse events are experienced in the first 6 month of treatment.

The increased rate of GI disorders was recently assessed in the II/005 variation (positive opinion adopted in October 2009) and the SmPC was reworded. Elevation of hepatic enzymes was already found to be an adverse event of special interest during initial assessment for MAA. Warning statements are already implemented in the SPC and PIL and are seen as sufficient.

SAEs most frequently were the following: infections (mainly pneumonia), injury and poisoning (primarily fractures of various types), neoplasms, GI disorders, nervous system disorders and cardiac disorders. Infections and infestations, the most frequently reported SAEs occurred more frequent in the higher dose group. Neoplasms were more frequent in the TCZ 4 mg/kg + MTX group (2.5%) than in the TCZ 8 mg/kg + MTX group (0.3%).

The rates of death remain unchanged compared to the previous evaluation. Further assessment of immunogenicity remains important and is addressed in the context of the Risk Management Plan. As part of the MAA the performance of the assay was discussed. A poor performance of the anti-drug antibody assay could easily explain the finding that infusion reactions are not associated with anti-TCZ antibodies.

The overall profile of infections was consistent with data reported previously. Most commonly reported were upper respiratory tract and urinary tract infections.

Update of Warnings and Precautions section to include information on viral reactivation reported with RA biologic therapies.

3.4 Pharmacovigilance aspects

Risk Management Plan

The MAH has submitted an updated RMP (version 7.0) with this Type II variation application. The latest version of the RMP has been updated in August 2009 (RMP version 5.0) to include a more appropriate wording with regard to GI perforations and agreed that these are useful and necessary changes.

Since submission of the last EU RMP, several changes have been made to the Core Data Sheet (CDS version 2 and CDS version 3) based on the cumulative safety data through 6 February 2009 from the TCZ safety database for ongoing studies in RA. The new safety information added to the CDS included the update of Warnings and Precautions section to include information on viral reactivation reported with RA biologic therapies. Section 4.4 of the SPC has been updated accordingly and reads as follows: "Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for rheumatoid arthritis. In clinical studies with tocilizumab, patients who screened positive for hepatitis were excluded". This change is endorsed by the CHMP.

Below, a list of all ongoing safety concerns is presented.

Summary of activities for each safety concern

Safety Issue	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Identified Risks:		
Serious infections	• Routine pharmacovigilance • Special CRF for events of special interest: implemented in clinical trials as of Q4 2007/Guided Questionnaire (post-marketing data) • Ongoing clinical trial •Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry	Routine risk minimization by means of labelling (SmPC sections 4.3, 4.4 and 4.8)
Complications of diverticulitis (including GI performation)	• Routine pharmacovigilance • Guided Questionnaire (postmarketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) • US registry	Routine risk minimization by means of labelling (SmPC sections 4.4 and 4.8)

Safety Issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
Serious hypersensitivity	• Routine pharmacovigilance • Guided Questionnaire (postmarketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry	Routine risk minimization by means of labelling (SmPC sections 4.4 and 4.8)
Neutropenia	• Study to address mechanism of neutrophil reduction • Routine pharmacovigilance • Guided Questionnaire for events of special interest will collect neutrophil data in cases of serious infection • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board	• Study ML25243 • Routine risk minimization by means of labelling (SmPC sections 4.2, 4.4 and 4.8)
Thrombocytopenia	• Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling (SmPC sections 4.2, 4.4 and 4.8)
Elevated hepatic transaminases	• Routine pharmacovigilance • Guided Questionnaire (postmarketing data) to collect information on serious hepatic events • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Nature and frequency of hepatic events representing potential clinical manifestations of increased transaminase levels will be monitored in the registry studies: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry	Routine risk minimization by means of labelling (SmPC sections 4.2, 4.4 and 4.8)
Immunogenicity	Routine pharmacovigilance • Ongoing clinical trial programme • Post-approval commitment to collect antibody titre data on all patients who experience immune-mediated AEs and those who have had a dosing holiday • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling (SmPC sections 4.8)

Safety Issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
Elevated lipids	Study WA19923 evaluating the effects of IL-6 receptor blockade with tocilizumab (TCZ) on lipids, arterial stiffness, and markers of atherogenic risk in patients with moderate to severe active RA • Routine pharmacovigilance • Ongoing clinical trial programme • Guided Questionnaires on implications of elevated lipids: ischaemic cardiovascular events (e.g., MI/acute coronary syndrome) and implications of elevated lipids: cerebrovascular events (e.g., stroke) • Regular review by Roche Pharmacoepidemiology Board • Rate of clinical events potentially related to atherogenesis (e.g. angina, MI, cerebrovascular accident) as a potential clinical manifestation of increased lipid levels will be monitored in the registry studies. The nature and rate of such events will be monitored and evaluated on the basis of reports to the: o Routine pharmacovigilance o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry	Routine risk minimization by means of labelling (SmPC sections 4.4 and 4.8)
Malignancies	• Routine pharmacovigilance • Guided Questionnaire (postmarketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry	Routine risk minimization by means of labelling (SmPC sections 4.4 and 4.8)
Demyelinating disorders	• Routine pharmacovigilance • Guided Questionnaire (postmarketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry	Routine risk minimization by means of labelling (SmPC sections 4.4)
CYP450 enzyme normalisation	Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling (SmPC sections 4.5)
Missing Information		

Safety Issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
Mortality in the Japanese PMS (RA indication)	Routine pharmacovigilance • Regular review by Roche • Semiannual review with PSURs (more frequently as warranted) – frequency to be re-examined after PSUR No. 4 • Pharmacoepidemiology Board	The ongoing Japanese PMS safety data are updated on Chugai's website on a monthly basis. The data are available to prescribers and patients in Japan.
Elderly patients	Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry	Routine risk minimization by means of labelling (SmPC sections 4.2)
Paediatric patients	Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board •Off-label use managed under compassionate use programme • Additional studies on efficacy and safety in paediatric patients: o Study WA18221 (SJIA) o Study WA19977(PJIA)	Routine risk minimization by means of labelling (SmPC sections 4.2)
Effects during pregnancy	• Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Registry study with OTIS • Pregnancy data from BSRBR and RABBIT	Routine risk minimization by means of labelling (SmPC sections 4.6)
Hepatic impairment	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling (SmPC sections 4.2, 4.4 and 5.2)
Renal impairment	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling (SmPC sections 4.2 and 5.2)
Combination with biologics	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry	Routine risk minimization by means of labelling (SmPC sections 4.4)
Vaccinations	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board • Plans for dedicated substudy under discussion	Routine risk minimization by means of labelling (SmPC sections 4.4)

3.4 Benefit Risk Assessment

The MAH has provided sufficient data to support the proposed changes to the SPC, especially to include a statement in section 4.1 of the SmPC that RoActemra has been shown to slow progression of joint damage and to improve physical function.

The MAH was asked to change Section 4.1 of the SmPC from "RoActemra has been shown to inhibit progression of joint damage…." to "RoActemra has been shown to **reduce** the rate of progression of

joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate."

This statement is based on one and 2 year x-ray data assessment, assessment of the change in HAQ-DL and facilitated by other patient reported outcomes as FACIT-fatigue and SF-36 physical function scores. Treatment with TCZ 8 mg/kg + MTX resulted in a 74% inhibition of progression of joint damage compared to placebo + MTX, as indicated by the mean change in total Sharp-Genant score from baseline to week 52. This inhibition was maintained (≥ 81%, from baseline) to week 104.

Patients treated with TCZ 8 mg/kg + MTX had a significant improvement in physical function at week 52 compared with placebo + MTX, as indicated by the AUC of the change in HAQ-DI, and this was maintained until week 104.

Treatment effects in signs and symptoms achieved at year 1 following treatment with TCZ 8 mg/kg + MTX were maintained (ACR50 and 70 responses) or showed further improvement (tender and swollen joint counts) at year 2. Response rates to therapy with TCZ 8 mg/kg (with or without concomitant DMARD) were maintained or improved with duration of treatment (ACR50, ACR70 and DAS28 remission) over time.

In the MAA, identified risks with TCZ treatment were serious infections (including opportunistic infections and infections with possibly fatal outcome), serious hypersensitivity reactions, and complications of diverticulitis, including lower gastrointestinal perforation. Potential risks with TCZ treatment were identified with regard to neutropenia, thrombocytopenia, elevations in hepatic transaminases and lipid parameters, and immunogenicity.

The overall rate of serious infections in TCZ-treated patients (4.66 per 100 patient-years) and the highest rates observed in the All Control population (TCZ 8 mg/kg, 4.9 per 100 patient-years) were both within the rates reported in the literature for other biologic treatments for RA (5.32 per 100 patient-years. The serious infection rate remained stable over time and the pattern of serious infections was consistent with that reported previously.

Serious infections occurred at a higher rate in patients > 65 years of age, patients in the higher weight and highest and lowest BMI categories, patients with prior co-morbidities that predispose them to infections (diabetes, chronic pulmonary disease), patients who previously received anti-TNFs and patients taking background corticosteroids; the highest rates were observed in the TCZ 8 mg/kg group.

In general Tocilizumab was well tolerated and the safety aspects were comprehensively characterised by the MAH. Given the nature of RA and the treatments available this product has an adequate safety profile with no reasons for concerns so far over a treatment period of longer than 2 years.

Overall, adverse effects associated with the mechanism of IL-6R inhibition (increased infections, neutropenia) were observed in all TCZ treatment groups. Additional safety aspects (gastrointestinal disorders, skin disorders, increases of hepatic transaminases, platelet decreases, increases in lipids) show a slight higher proportion in the 8mg/kg dosing regimen compared to the 4 mg/kg regimen. These aspects are adequately addressed in the proposed SmPC.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

The following additional risk minimisation activity was required: The MAH will conduct study ML25243 to elucidate mechanism of reductions in neutrophil count.

2. Conclusion

On 22 April 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Annex IIIB.