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STATISTICAL REVIEW(S)



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OFFICE OF TRANSLATIONAL SCIENCES
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Statistical Review and Evaluation CLINICAL STUDIES

BLA: 125276

Name of drug: ACTEMRA (tocilizumab)

Indication: Treatment of adult patients with moderate to severe active rheumatoid arthritis alone or in combination with methotrexate or other disease modifying anti-rheumatic drugs

Applicant: Hoffman-La Roche Inc.

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The Applicant, Hoffman-La Roche, seeks to market ACTEMRA for the treatment of patients with adult onset rheumatoid arthritis (RA).

The evidence taken collectively from studies reviewed indicated statistical support in favor of tocilizumab 8 mg/kg either as a monotherapy or a combination therapy in the reduction of signs and symptoms of RA after 24 weeks of therapy. Based on the weekly responder analyses of the ACR20 response in all five studies, some patients experienced an improvement in ACR20 response as early as Week 2, which persisted throughout the study (i.e. Week 24).

There is also evidence that tocilizumab 4 mg/kg in combination with MTX therapy is associated with reduction in signs and symptoms of RA after 24 weeks of therapy. Although there was no direct statistical comparison, there is some evidence that the effect was consistently lower than that of the TCZ 8 mg/kg group.

There is also enough evidence that tocilizumab demonstrated effects on ACR50 and ACR70 in the various patient populations studied. In addition, changes from baseline for each of the ACR core set parameters are also consistent with the composite scores

I defer discussion on the clinical relevance of the treatment differences as well as the dosing regimen to Dr. Okada. In addition, the reader is also referred to Dr. Okada's review for more detail of the rationale behind the decision to exclude the results from the analyses of patient-reported outcomes (using the SF36 and FACIT-F questionnaires), patient's disease activity (DAS28), as well as the hemoglobin levels in the label.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In all five studies, patients who were > 18 years of age with active rheumatoid arthritis diagnosed according to the American College of Rheumatology criteria, as well as having at least 8 tender and 6 swollen joints at baseline were included in the study. The objectives of these studies were similar. All studies were designed to assess safety and reduction in the signs and symptoms of RA after 24 weeks of TCZ as monotherapy (Study WA17824), in combination with MTX (Studies WA17822 and WA17823) or other DMARDs (Study WA18063) in patients with inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to TNF antagonist (Study WA18062), see Section 3.1.1 for more detail.

1.3 STATISTICAL ISSUES AND FINDINGS

I did not identify any statistical issues in the BLA submission that could not be resolved by recoding and re-analyzing the data. For example, I identified various discrepancies between the raw and derived datasets. These discrepancies were found not to affect the overall conclusion.

The following are the key findings of the study:

1. There is sufficient evidence from all four clinical studies (Studies WA17822, WA17823, WA18062 and WA18063) that a higher proportion of patients in the tocilizumab 8 mg/kg

group (in combination therapy) achieved ACR20 response compared to the placebo group (in combination therapy). In the direct comparison between tocilizumab 8 mg/kg monotherapy and MTX dose escalated to 20 mg/wk within 8 weeks (Study WA17824), there is evidence that tocilizumab therapy is superior to MTX therapy.

2. There is also consistent evidence that a higher proportion of patients in the tocilizumab 4 mg/kg in combination with MTX therapy achieved ACR20 response compared to the placebo + MTX therapy. The effect is consistently lower than that of the TCZ 8 mg/kg group.
3. In terms of ACR50 and ACR70 responses, tocilizumab consistently demonstrated greater effects compared to the comparator group (i.e. placebo or MTX monotherapy) in various patient populations studied. Changes from baseline for each of the ACR core set parameters are also consistent with the composite scores
4. Except in Study WA18062, a separation between the tocilizumab combination therapy and monotherapy groups and the comparator groups in ACR20 response rates is apparent at week 2. In study WA18062, the separation is most apparent at week 4. At all time points after week 2, the greatest response rates are observed in the tocilizumab 8 mg/kg + MTX group (Studies WA17822, WA17823, and WA18062).
5. As part of the exploratory analysis, HAQ-DI responder analysis was conducted. Responder is defined as patients who had at least 0.22 unit decreased in HAQ-DI score from baseline at the end of week 24. A larger proportion of HAQ-DI responders among patients treated with either tocilizumab with background MTX (Studies WA17822, WA17823 and WA18062), or tocilizumab with background DMARD (Study WA18063) are observed in comparison to patients treated with placebo (with background MTX, or with background DMARD), regardless of the tocilizumab dose. In addition, there is also higher proportion of HAQ-DI responder among patients treated with tocilizumab monotherapy compared to MTX alone (Study WA17824).
6. Considering that the open-label extension studies were ongoing and only a partial amount of information is available, it is difficult to assess whether patients who are ACR20 responder at Week 24 during the core studies (i.e. double-blind phase) maintained their responder status over a period of 18 months. Therefore, there is no sufficient information at this time to evaluate the claim of 'maintenance of effect'.
7. In terms of treatment by subgroup analysis, there is no consistent evidence of treatment by subgroup interaction across the five studies. It appears that 'region' may have an effect on treatment group differences, but so far, this is only evident in one MTX combination study (Study WA17822) and one DMARD combination study (Study WA18063). However, according to Dr. Okada, this finding is consistent with the other biologic products approved for the same indication. Furthermore, because the effect in North America remains positive and consistent with the overall conclusion, the regional differences are less worrisome.

2 INTRODUCTION

2.1 OVERVIEW

The Applicant, Hoffman-La Roche, seeks to market ACTEMRA for the treatment of patients with adult onset rheumatoid arthritis (RA). The proposed indication is:

ACTEMRA (tocilizumab) is indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who are naïve to treatment with, or who had an inadequate response to, one or more disease modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor α (TNF) antagonists. ACTEMRA can be used alone or in combination with methotrexate (MTX) or other DMARDs.

ACTEMRA 8 mg/kg is administered by intravenous infusion every 4 weeks alone or in combination with MTX or other DMARDs.

The clinical development program includes data on 3192 patients receiving at least one dose of 8 mg/kg ACTEMRA, including 2570 exposed to 8 mg/kg for greater than 6 months, 1443 exposed to 8 mg/kg for greater than 1 year, and 554 exposed to 8 mg/kg for greater than 18 months. This was conducted with a co-development partner, Chugai Pharmaceutical Co. Ltd. ACTEMRA is approved in Japan for the treatment of Castleman's Disease and Chugai has submitted a supplemental NDA in Japan for the treatment of patients with adult onset RA and systemic-onset of juvenile idiopathic arthritis based on studies completed in Japan.

The development plan for ACTEMRA (tocilizumab) was introduced to the Division of Therapeutic Biologics Internal Medicine Products under BBIND11972. Following the reorganization of the therapeutic areas in the Center for Drug Evaluation and Research, tocilizumab fell under the purview of the Division of Anesthesia, Analgesia and Rheumatology Products. The key milestones in the clinical development program are highlighted in Dr. Okada's review. This includes key interactions with the Agency from September 9, 2004 through October 9, 2007. Statistical issues were discussed during several meetings and key issues are summarized below:

1. Pre-Phase 3 meeting (September 9, 2004)

Primary Endpoints:

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1. Sponsor should consider another endpoint in place of the HAQ AUC or as an additional secondary analysis comparing the percentage of subjects with a clinically meaningful improvement in HAQ (e.g. >0.3 units) at 6 and 12 months (i.e. responder analysis).
 2. Sponsor should include the proportion of subjects achieving a major clinical response (ACR70 maintained at ≥ 6 months) as a secondary endpoint.

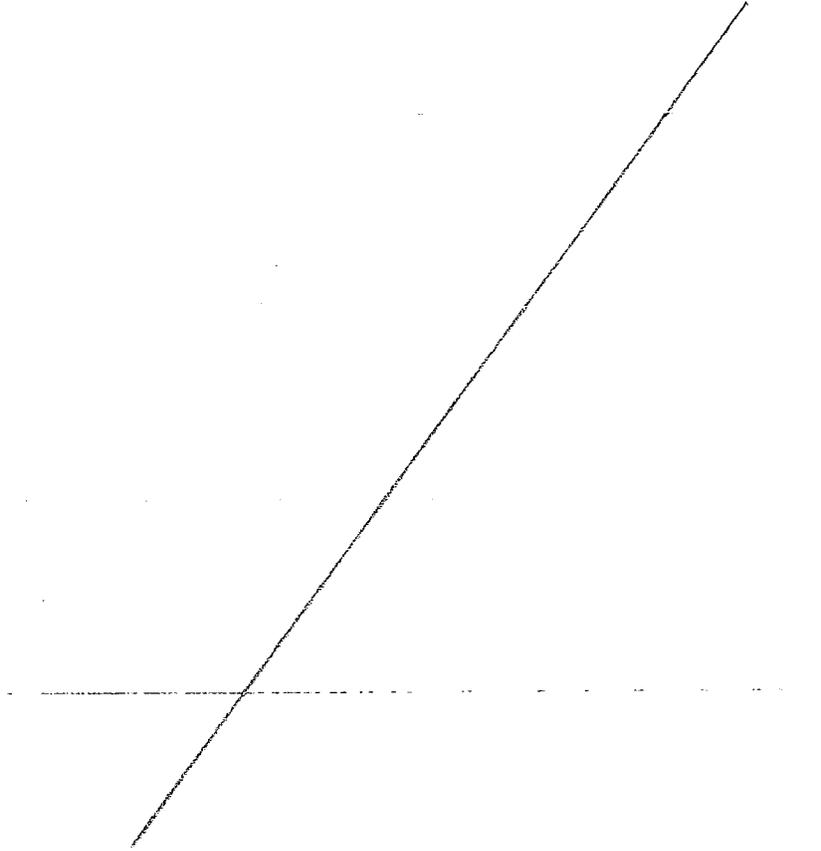
3. Sponsor should define the term 'no erosions' as a change in total Sharp score ≤ 0 units and not as the smallest detectable difference.

Blinding

Joint counts should be assessed by blinded, independent joint assessors.

Statistical Analysis Plan

The following are suggestions given during the meeting:



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2. Telecon (September 8, 2005)

The following comments to the data reporting and analysis manual (DRAM) were provided to the Sponsor:

The approach to multiple testing in Studies 17822, 17823 and 18062 provided by the Sponsor is adequate for type 1 error rate. However, it is not clear what significance results

will be used to make the claim. Claim can be based on comparison between each dose and placebo not on a combined comparison. The Division cautioned that decision rule has the following potential risks:

- a. If null hypothesis is not rejected in the test for the combined groups then it is not permissible to continue even if an informal assessment suggests that one of the dose groups vs. placebo comparisons is significant.
- b. If null hypothesis is rejected in the test for the combined groups there still may be no sign between any dose groups and placebo.
- c. The proposed method of pooling the two dose groups in the test may reduce the statistical power in the event that one of the dose groups is similar to or worse than the placebo in the endpoint to be tested.

The Division also reminded the Sponsor to justify the non-inferiority margin of -0.12% to be used in Study WA17824.

3. Statistical Analysis Plan (November 1, 2006 under serial # 292)

The following were comments and recommendations provided to the Sponsor.

- a. The analysis plan should additionally include pre-specified analyses for the "Change from baseline in Modified Sharp total radiographic score at Week 52 (12 months) and at Week 104 (24 months)" and the "Change in physical function as measured by the area under the curve for the change from baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) at week 52 and at week 104" in Study WA17823.
- b. The proposed sample size for each study is acceptable. Of note, the Division's assessment of efficacy will evaluate the statistical significance and clinical meaningfulness of the treatment effect.

4. Pre-BLA Format and Content (May 7, 2007)

The comments relate to the BLA format and content. We requested that the data collection page (blankcrf.pdf) be hyperlinked to the data definition file (define.pdf) for each variable coming from the raw data.

The Division also commented that the Sponsor does not need to provide the SAS program in the BLA, but the Division may request the program during the review.

5. pre-BLA (September 12, 2007)

- a. The Division noted that the proposal to pool the efficacy data by treatment group for Studies WA17822, WA17823 and WA18063, as well as pooling the 6-month safety data for analyses are acceptable.
- b. The BLA should include an analysis of safety and efficacy by body weight and by body mass index, as well as subset analyses for the primary endpoint by baseline demographics, baseline disease characteristics, and investigational site.
- c. The Division also provided several recommendations on the analysis of safety data.

This submission included five randomized, double-blind, placebo-controlled studies and two open-label long-term extension studies. Key characteristics of the studies are summarized in Table 1.

Table 1: Key Features of the Phase 3 studies

Design and Duration	WAI17822	WAI17823	WAI17824	WAI18062	WAI18063	WAI18695	WAI18695
Patient Population	Moderate to severe active RA in MTX inadequate responders	Moderate to severe active RA in MTX inadequate responders	Active RA; MTX naive or MTX discontinued but not due to lack of efficacy or toxic effect	Moderate to severe active RA in patients with inadequate response to anti-TNF agent(s)	Moderate to severe active RA in patients with inadequate response to DMARDs	Patients completing treatment in WAI17822	Patients completing treatment in WAI17824, WAI18062, WAI18063, WPI18663
Treatment	3 arm study: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks + MTX 10-25 mg/week	3 arm study: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks + MTX 10-25 mg/week	2 arm study: Tocilizumab: 8 mg/kg iv every 4 weeks or MTX 7.5-20 mg/week (po) Substudy includes 3 rd arm: Placebo (8 weeks placebo then 16 weeks TCZ 8 mg/kg)	3 arms: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks plus MTX 10-25 mg/week	2 arms: Tocilizumab: 8 mg/kg or placebo iv every 4 weeks plus standard DMARD(s)	1 arm: Tocilizumab: 8 mg/kg iv every 4 weeks plus MTX	1 arm: Tocilizumab: 8 mg/kg iv every 4 weeks alone or plus MTX / other DMARD(s)
Escape therapy	Week 16: TCZ 8 mg/kg	Week 16 onwards: TCZ 4 or 8 mg/kg	Substudy only, up to Week 8: TCZ 8 mg/kg	Week 16: TCZ 8 mg/kg	Week 16: adjustment of background DMARD		
Total Randomized Patients	623	1196	673	499	1220	537**	1902**
Primary Endpoint at Week 24	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	Long term safety/efficacy	Long term safety/efficacy

DB = double blind, R = randomized, PC = placebo controlled, DD = double dummy, OL = open label
 * Or when tocilizumab becomes commercially available in the participating country, or when the sponsor decides to discontinue the study.
 ** Patients were not randomized into WAI18695 and WAI18696, but enrolled from studies WAI17822, WAI18063, WAI18062 and WAI17824

2.2 DATA SOURCES

This statistical review is based on data submitted in studies WA17822, WA17823, WA17824, WA18062, and WA18063.

The electronic submission of this BLA can be found at:
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3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The clinical program of ACTEMRA comprised five double-blind, placebo-controlled studies and two long-term safety studies. Throughout the review, tocilizumab will be referred to as TCZ, methotrexate as MTX, and disease modifying anti-rheumatic drugs as DMARDs.

3.1.1 STUDY DESIGN AND ANALYSIS PLAN

In all five studies, patients who were > 18 years of age with active rheumatoid arthritis diagnosed according to the American College of Rheumatology criteria, and had at least 8 tender and 6 swollen joints at baseline were included in the study. The objectives of the studies were similar.

The primary efficacy objective of studies WA17822, WA17823 and WA18062 was to assess the efficacy of TCZ vs. placebo in patients with moderate to severe active RA with regard to reduction in signs and symptoms over 6 months of treatment in combination with background MTX therapy. Studies WA17822 and WA17823 were conducted in patients with an inadequate clinical response to MTX and study WA18062 was conducted in patients who had had inadequate response to one or more anti-TNF therapies.

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

The primary objective of study WA17824 was to assess the efficacy of TCZ monotherapy vs. MTX in patients who had not been treated with MTX within 6 months prior to randomization and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response (as determined by the investigator).

With the exception of WA17823, all studies had a 24-week treatment period and the primary endpoint was the proportion of ACR20 responders at week 24. In order to achieve an ACR20 response, a patient was required to have at least a 20% improvement compared with baseline, in both tender and swollen joint counts (TJC and SJC, respectively), as well as in 3 out of 5 additional ACR core set variables: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI) and the acute phase reactants (i.e. C-Reactive Protein (CRP)). CRP was used primarily for the calculation of the ACR response; if missing, erythrocyte sedimentation rate (ESR) was substituted.

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

Study WA17824 was designed to demonstrate non-inferiority against MTX and included a 3-arm randomized, double-blind, double-dummy, parallel-group substudy with a placebo arm (8 weeks of placebo treatment followed by 16 weeks of TCZ 8 mg/kg) as an internal control for efficacy.

In all studies, randomization was stratified by site. In addition, study WA17824 was stratified by disease duration (≤ 2 years versus > 2 years).

In studies WA17822, WA17823, and WA18062, randomization was in a 1:1:1 ratio and patients in study WA18063 were randomized in a 2:1 ratio (TCZ:placebo), see Table 2. The Applicant states,

In the MTX studies (Study WA17822, WA17823, and WA18062), all patients had to have received MTX for > 12 weeks before randomization with at least 8 weeks prior to baseline being at a stable dose of between 10 – 25 mg/week. Meanwhile, in Study WA18063, patients had to have been on stable doses of permitted DMARDs for at least 8 weeks prior to baseline. They could be used alone or in combination, except for the combination of MTX and leflunomide, which was not permitted. In all four studies, TCZ doses were to remain stable during the treatment period; however, MTX dose reductions or a change in route of administration could be performed at any time for safety reasons.

Patients in study WA17824 were randomly assigned in a 1:1 ratio to either TCZ 8 mg/kg or MTX, and in the substudy, patients were randomly assigned in 1:1:1 ratio to either TCZ 8 mg/kg or MTX (as in the main study), or to receive placebo MTX weekly plus iv placebo every 4 weeks for 8 weeks (2 infusions). All patients in the substudy continued with TCZ 8 mg/kg as an intravenous infusion every 4 weeks for the remaining 4 months of the study. In order to maintain the blind, patients continued to receive placebo MTX capsules. According to the Applicant,

One 5 mg (2.5 mg capsules) reduction in medication (MTX or its placebo) was permitted for patients who, in the opinion of the treating physician, experienced dose-limiting MTX-related side effects. The dose could not be increased at any time after the dose had been reduced nor could it be reduced to less than 4 capsules/week (10 mg).

Table 2: Trial Medication Route and Regimen

Study Drug	Route	Background therapy	Route
Studies WA17822, WA17823 and WA18062			
TCZ 4 mg/kg every 4 weeks	IV	MTX 10-25 mg/week	Oral or parenteral
TCZ 8 mg/kg every 4 weeks	IV	MTX 10-25 mg/week	Oral or parenteral
Placebo every 4 weeks	IV	MTX 10-25 mg/week	Oral or parenteral
Study WA18063			
TCZ 8 mg/kg every 4 weeks	IV	Stable DMARD alone or in combination	Oral or parenteral
Placebo every 4 weeks	IV	Stable DMARD alone or in combination	Oral or parenteral
WA17824			
Study Drug	Route	Placebo	Route
TCZ 8 mg/kg every 4 weeks	IV	Weekly	Oral
MTX 7.5-20 mg / week (escalating dose)*	Oral	Every 4 weeks	IV
Placebo TCZ every 4 weeks for 8 weeks; then active TCZ 8 mg/kg every 4 weeks**	IV	Placebo MTX weekly	Oral

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

** In the WA17824 substudy only.

Source: Clinical Summary of Efficacy, page 38

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

In studies WA17822, WA17823, WA18062 and WA18063 patients who had a < 20% improvement in TJC and SJC from baseline at week 16 could receive escape therapy consisting of the following:

- In studies WA17822 and WA18062, patients received TCZ 8 mg/kg.
- In study WA17823, escape therapy with TCZ was administered in steps and was allocated in a blinded fashion using an interactive voice response system (IVRS). In the first step, patients in the TCZ 4 mg/kg and 8 mg/kg groups received TCZ 8 mg/kg and patients in the placebo group received TCZ 4 mg/kg. If after ≥ 12 weeks on escape therapy, patients had still not achieved a $\geq 20\%$ improvement from baseline in SJC and TJC, patients in all groups could receive a second escape therapy step of TCZ 8 mg/kg.
- In study WA18063, patients could have the dose of background DMARD adjusted and/or be provided treatment with different traditional DMARDs. Patients did not receive TCZ as escape therapy.

In study WA17824, only patients at sites participating in the placebo-controlled substudy were eligible to receive escape therapy. Patients in the substudy could receive escape therapy of TCZ 8 mg/kg if they had a $\geq 20\%$ worsening from baseline in SJC and TJC at any visit prior to (but not including) week 8. MTX/MTX-placebo capsules were discontinued when a patient received escape therapy.

In all of the pivotal Phase III studies, escape patients could also receive intra-articular corticosteroids or an increase in oral corticosteroid dosage (maximum dose of 10 mg total dose/day).

Efficacy data were analyzed for the intent-to-treat (ITT) and per protocol (PP) population.

The ITT population was defined as all randomized patients who received at least one administration of study medication, and was the primary analysis population for all of the Phase III studies except WA17824, which was intended to demonstrate non-inferiority, so the PP population was the primary analysis population. The PP population included patients who met certain inclusion and exclusion

criteria and did not have post-randomization violations that were deemed to have the potential to affect patient outcome in terms of efficacy.

In Study WA17824 (non-inferiority study), the primary analysis population is the PP population. According to the ICH E-9 document,

Subjects who withdraw or drop out of the treatment group or the comparator group will tend to have a lack of response such that it will generally diminish the treatment effect; hence the results of using the full analysis set (i.e. ITT population) may be biased toward demonstrating equivalence (or non-inferiority).

For the four placebo-controlled studies (WA17822, WA17823, WA18062 and WA18063), the statistical hypotheses were based on a superiority comparison against the control (placebo + DMARD) in the proportion of patients with an ACR20 response at Week 24. A two-sided 5% significance level was used throughout the analyses. The primary analysis was the Cochran-Mantel-Haenszel chi-squared test with adjustment for the stratification factor applied at randomization. This was performed using the pre-defined primary and secondary methods for handling missing data (Table 3). Of note, the primary method is the application of non-responder outcome to all patients with missing data (e.g. those who entered escape or who discontinued therapy prior to Week 24 regardless of the reason). Because only the result from the interim week 24 analyses was included in this submission for Study WA17823, the methods used to analyze the modified Sharp total radiographic score and physical function score were not provided (see Table 4).

For Study WA17824, the statistical hypothesis was based on a non-inferiority comparison of the TCZ 8 mg/kg arm against MTX using the extended Mantel-Haenszel statistic. The extended Mantel-Haenszel approach calculates the weighted difference in proportion between the two treatment groups, adjusted for site and disease duration. For a full detail of the approach, see Appendix 1. The null hypothesis was rejected if the lower limit of the two-sided 95% confidence interval (CI) for the difference in the proportion of ACR20 responders on TCZ minus MTX was ≥ -0.12 . However, if the lower limit of the 95% CI for the treatment difference was > 0 , then the corresponding p-value for superiority was also produced for the comparison of ACR20, ACR50 and ACR70. In addition, to support the conclusions from the primary analysis, a comparison was made between the TCZ treatment group and the placebo group in the substudy. The null hypothesis tested by this comparison was that the proportion of patients with an ACR20 response at week 8 in the TCZ treatment arm was equal to the proportion of patients with an ACR20 response at week 8 in the placebo arm. This null hypothesis was rejected if the lower limit of the two-sided 95% CI for the difference in the proportion of ACR20 responders on TCZ minus placebo was greater than zero.

In the September 9, 2004 pre-Phase 3 meeting and the September 8, 2005 teleconference with the Applicant, the Division requested submission of a complete proposal outlining the rationale for choosing a 12 percentage point confidence interval for the proposed non-inferiority trial analyzing TCZ 8 mg/kg vs. MTX alone. On November 1, 2006, the Sponsor submitted their statistical analysis plan for all five studies (under serial no. 292), and in that submission provided the following justification for the non-inferiority margin for the monotherapy study (WA17824).

This non-inferiority limit of 12% is based on several considerations, both statistical and clinical. The proposed limit is approximately 50% of the difference between methotrexate (MTX) and placebo. This is based on an ACR20 response rate for MTX-naïve patients at 6 months of about 50% and a placebo response of about 27% from the same study. Therefore, 12% is approximately half the difference between MTX and placebo. There is evidence in literature for an average placebo response across trials of about 30% and a conservative estimate of ACR20 response rate for MTX, based on the literature, would be about 55% with 12% again being approximately half the difference.

A review of biologic and DMARD monotherapy trials reveals that the ACR20 response rate at 6 months varies from 43 – 70%. This wide variation in response rates does not seem, of itself, to influence physicians in their choice of an agent to treat rheumatoid arthritis. It would appear that what most influences the choice of an agent is the potential and actual response of a particular patient to a particular drug. The choice of a drug is based on the individual patient, provided that there is good evidence that a drug is potentially effective, and it is not based on overall levels of effectiveness in large groups. For TCZ monotherapy to be considered of benefit to patients strong evidence of effectiveness in comparison to established placebo rates of about 30% is required and there is a need to demonstrate that the effectiveness of TCZ falls within the ranges of other monotherapy DMARDs as shown in the trials cited above. The 12% difference proposed in the monotherapy study is minor from a clinical standpoint and is less than the range of responses in the monotherapy trials listed above. Since even the broader ranges of response cited do not appear to influence physician choice, a 12% limit would be considered acceptable and justifiable by clinicians.

According to Dr. Okada, this margin is acceptable.

In studies WA17822, WA17823 and WA18062, which have two TCZ treatment arms plus a control arm, a sequential testing procedure was produced for the primary endpoint so that the TCZ 8 mg/kg arm was first compared with the placebo arm, and only if this comparison resulted in a p-value of ≤ 0.05 was a comparison of the TCZ 4 mg/kg with placebo performed.

In each of the study, the Applicant proposed to explore several secondary endpoints (Table 5). In order to control the rate of false positive conclusions resulting from multiple secondary endpoints, a prospectively-defined fixed sequence approach was applied to statistical testing for each individual study (Appendix 2). This approach allowed the testing of each of the null hypotheses for each secondary endpoint at the same significance level of a (5%) without any adjustment, as long as the null hypotheses were tested in a pre-defined hierarchical order. No confirmatory claims were to be based on endpoints that have a rank lower than or equal to that variable whose null hypothesis was the first that could not be rejected.

Table 3: Primary Endpoint Analyses (Studies WA17822, WA17823, WA17824, WA18062, and WA18063)

Endpoint(s)	Patient population	Analytical approach	Missing Data Imputation
Proportion of patients with an ACR20* response at Week 24	Intent-to-treat † (primary) Per protocol ‡ (secondary)	<p>Primary: Cochran-Mantel-Haenszel chi-squared test** with adjustment for the stratification factor applied at randomization.</p> <p>Secondary:</p> <ul style="list-style-type: none"> - logistic regression including the stratification factor(s) applied at randomization in the model. - Time to first ACR20 using Kaplan-Meier estimates - Generalized estimating equations to compare the longitudinal probability of an ACR 20 response between treatment groups. The primary model will include: site (or region), treatment group, visit and treatment group by visit interaction. <p>For WA17824, an extended Mantel-Haenszel statistic adjusting for the stratification factor(s) applied at randomization will be applied for the difference in proportion of ACR20 responders to produce a 95% confidence interval. The null hypothesis will be rejected if the lower limit of the two-sided 95% confidence interval for the difference in the proportion of ACR20 responders on TCZ minus MTX is ≥ -0.12.</p>	<p>Primary:</p> <ul style="list-style-type: none"> - Patients who withdrew prematurely from the study will be classed as non responders from the date they withdrew. - Patients who receive escape therapy will be classed as non responders for all time points beyond the time point at which they first receive escape therapy. - Patients that do not have the required data (i.e. tender and swollen joint counts, and at least three of the five ACR core set variables) at baseline and at that specific time point will be classed as non responders at that time point. - Patients that have had intra-articular injections of steroid within the 8 weeks prior to their week 24 assessment will classed as non responders at Week 24 only. <p>- The tender and swollen joint counts will use the total derived using the last observation carried forward method (LOCF).</p> <p>- C-reactive protein (CRP) will be used primarily for the calculation of the ACR response, if missing, erythrocyte sedimentation rate (ESR) will be substituted.</p> <p>- The physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, and HAQ-DI components will be based on the raw results.</p> <p>Secondary:</p> <ul style="list-style-type: none"> - LOCF for each of the components - For escape patients, value at the escape visit or if missing the last pre-escape/post baseline value will be carried forward - For withdrawal patients, value at the withdrawal or if missing, last efficacy assessment prior to withdrawal will be carried forward.

Source: Sponsor's submission package

* A positive ACR20 response requires at least a 20% improvement compared to baseline in both tender and swollen joint counts, as well as in 3 out of 5 of the additional ACR core set variables: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI) and an acute phase reactant (C-reactive protein, CRP), or Erythrocyte Sedimentation rate (ESR).

† The ITT analysis population will consist of all patients that are randomized and who receive at least one administration of study medication.

‡ The PP population will consist of patients meeting certain inclusion and exclusion criteria that have been deemed to have the potential to affect patient outcome in terms of efficacy.

** Only for Studies WA17822, WA17823, WA18062, and WA18063.

Table 4: Additional Endpoint Analyses for Study WA17823

Endpoint(s)	Patient population	Analytical approach	Missing Data Imputation
Change from baseline in Modified Sharp total radiographic score at Week 52 (12 months) and at Week 104 (24 months)	Intent-to-treat † (primary) Per protocol ‡ (secondary)	No information	
Change in physical function as measured by the area under the curve for the change from baseline in the Health Assessment Questionnaire Disability Index at week 52 and at week 104.	Intent-to-treat † (primary) Per protocol ‡ (secondary)	No information	The primary method of analysis of the HAQ-DI score, no imputation of missing will be made, other than for missing baseline scores, for which last score prior to baseline will be carried forward.

Source: Sponsor's submission package

* A positive ACR20 response requires at least a 20% improvement compared to baseline in both tender and swollen joint counts, as well as in 3 out of 5 of the additional ACR core set variables: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI) and an acute phase reactant (C-reactive protein, CRP), or Erythrocyte Sedimentation rate (ESR).

† The ITT analysis population will consist of all patients that are randomized and who receive at least one administration of study medication.

‡ The PP population will consist of patients meeting certain inclusion and exclusion criteria that have been deemed to have the potential to affect patient outcome in terms of efficacy.

** Only for Studies WA17822, WA17823, WA18062, and WA18063.

Table 5: Secondary Endpoints

Study	Endpoint(s)	Patient population	Analytical approach
W/A17822 W/A17823* W/A17824 W/A18062 W/A18063	<ul style="list-style-type: none"> - Proportion of patients with an ACR50 and ACR70 responses at Week 24 - Mean changes from baseline in the individual parameters of ACR core set at 24 weeks. - AUC of the ACRn - Longitudinal (GEE) analysis of ACR20, ACR50 and ACR70 responses. - Change in disease activity score (DAS28) from baseline at 24 weeks. - Proportion of patients classified as categorical DAS28 responders (EULAR response) at 24 weeks. - AUC of the mean disease activity score - HAQ, SF-37 and FACIT fatigue scale scores at 24 weeks. - Proportion of patients who withdraw due to lack of sufficient therapeutic response. - Proportion of patients in each treatment group who receive escape therapy. - Mean change in RF (IU/mL) at 24 weeks in those patients with + RF. - Proportion of patients with DAS28 score < 2.6 at 24 weeks - Time to ACR20, ACR50, and ACR70 response. - Change in Hemoglobin from baseline at 24 weeks. 	Intent-to-treat † (primary) Per protocol ‡ (secondary)	Categorical variable: Cochran-Mantel-Haenszel chi-squared test** with adjustment for the stratification factor applied at randomization. Secondary: -logistic regression including the stratification factor(s) applied at randomization in the model. Continuous variable: Analysis of covariance Time to Analysis: Kaplan-Meier estimates Longitudinal data: Generalized estimating equation analysis
W/A17824	Additional: <ul style="list-style-type: none"> - The proportion of patients with an ACR20 response at Week 8. - Median time to improvement in daily pain VAS (25% decline in pain VAS from baseline). - Proportion of patients that achieved a remission according to the ACR remission criteria by Week 24. 	Intent-to-treat † (primary) Per protocol ‡ (secondary)	

Source: Sponsor's submission package
 *W/A17823: Endpoints at Week 24. Does not include Time to ACR20, ACR50, and ACR70 response, as well as Change in hemoglobin from baseline at 24 weeks.
 † The ITT analysis population will consist of all patients that are randomized and who receive at least one administration of study medication.
 ‡ The PP population will consist of patients meeting certain inclusion and exclusion criteria that have been deemed to have the potential to affect patient outcome in terms of efficacy.

Table 5: Secondary Endpoints (Continued)

Study	Endpoint(s)	Pt. Population	Analytical approach
WAI17823	<p>Endpoints post Week 24:</p> <ul style="list-style-type: none"> - Proportion of patients who achieve an improvement of at least 0.3 units from baseline in the HAQ disability index at 52 and 104 weeks. - Proportion of patients with ACR20, ACR50 and ACR70 responses at 52 and 104 weeks. - Proportion of patients with ACR70 response maintained for 6 consecutive months. - Mean changes from baseline in the individual parameters of ACR core set at 52 and 104 weeks. - AUC of the ACRn to 52 and 104 weeks - Longitudinal (GEE) analysis of ACR20, ACR50 and ACR70 responses to 52 and 104 weeks. - Change in disease activity score (DAS28) from baseline at 52 and 104 weeks. - Proportion of patients classified as categorical DAS28 responders (EULAR response) at 52 and 104 weeks. - Proportion of patients with DAS28 score < 2.6 at 52 and 104 weeks - AUC of the mean disease activity score at 52 and 104 weeks - Change from baseline in modified Sharp total radiographic score to weeks 24 and 80. - Change from baseline in erosion score to weeks 24, 52, 80, and 104. - Change from baseline in joint space narrowing score to weeks 24, 52, 80, and 104. - Proportion of patients with no progression of erosion by number of new erosions at 24, 52, and 104 weeks. - Proportion of patients with no progression of joint space narrowing by number of new joint space narrowing at 24, 52, and 104 weeks. - HAQ, SF-37 and FACIT fatigue scale scores at 52 and 104 weeks. - Mean change in RF (IU/mL) at 24 weeks in those patients with + RF. - Proportion of patients who withdraw due to lack of sufficient therapeutic response. - Proportion of patients in each treatment group who receive escape therapy. - Proportion of patients that achieved a remission according to the ACR remission criteria by Week 52 and 104. - Proportion of patients that achieved complete clinical response at Week 52 and 104. 	<p>Intent-to-treat † (primary) Per protocol ‡ (secondary)</p>	<p>Categorical variable: Cochran-Mantel-Haenszel chi-squared test** with adjustment for the stratification factor applied at randomization. Secondary: - logistic regression including the stratification factor(s) applied at randomization in the model.</p> <p>Continuous variable: Analysis of covariance</p> <p>Time to Analysis: Kaplan-Meier estimates</p> <p>Longitudinal data: Generalized estimating equation analysis</p>

Sample Size

The sample size for each study was determined based on the following assumptions:

In study WA17822, the sample size of 210 patients per arm (i.e. 630 patients in total) was determined to provide at least 90% power to detect treatment group difference of 20% (i.e. 60% ACR20 response in the TCZ/MTX group and 40% ACR20 response in the placebo/MTX group) based on the results from the LRO301 Phase 2 dose finding study. The sample size was determined using a two-sided test with $\alpha=0.03$ (because of multiple active arms) and a discontinuation rate of 15%.

In Study WA17823, the sample size of 390 patients per arm was determined based on several endpoints and assumptions:

1. Treatment difference on the change in sharp score from baseline to 12 months was assumed to be 3 units with a standard deviation of 11 units.
2. Treatment difference in the ACR20 response was assumed to be 20% (TCZ/MTX 50% ACR20 response and placebo/MTX comparator 30% ACR20 response).
3. Treatment difference on the change from baseline in HAQ disability index score of about 0.3 with a standard deviation of 0.5.

Given these assumptions, the planned 390 patients per treatment arm gives at least 90% power to detect a difference between TCZ/MTX group and placebo/MTX group. The sample size was determined using a two-sided test with $\alpha=0.0125$ (corrected for multiple comparisons of active arms and control) and a discontinuation rate of 15%.

In Study WA17824, data from Phase II studies of 8 mg/kg TCZ given as monotherapy suggest that the likely 24 week ACR20 response on this dose will be approximately 70%. Sample size and power calculations assuming a MTX rate of 65% and TCZ rate of between 66% and 70% show that a study recruiting 275 patients per arm will have at least 90% power to demonstrate TCZ non-inferior to MTX, using a 12 percentage point non-inferiority margin. The sample size was determined using an $\alpha=0.025$ (corrected for multiple comparisons of active arms and control)

In study WA18062, the sample size of 150 patients per arm (i.e. 450 patients in total) was determined to provide at least 80% power to detect treatment group difference of 20% (i.e. 50% ACR20 response in the TCZ/MTX group and 30% ACR20 response in the placebo/MTX group) based on the results from the LRO301 Phase 2 dose finding study. The sample size was determined using a two-sided test with $\alpha=0.03$ (because of multiple active arms) and a discontinuation rate of 15%.

In Study WA18063, a total of 1200 patients are planned to be allocated in a 2:1 ratio to the two treatment groups, TCZ 8 mg/kg (800) or placebo (400) i.v. every 4 week. This sample size was chosen in order to provide the required numbers of patients exposed to TCZ for the purposes of compilation of a safety database for registration. For the ACR20 response, this sample size (800:400) would give greater than 90% power to detect a difference between the TCZ and the Placebo arms at week 24.

3.1.2 PATIENT CHARACTERISTICS AND DISPOSITIONS

Patient Disposition

The number of patients who were randomized and included in the ITT and PP population is summarized in Table 6.

Table 6: Overview of Analysis Population (All Patients)

Study		Placebo	TCZ4mg/kg	TCZ8mg/kg	MTX
WA17822*	# of Patients Randomized	204	214	205	
	# included in ITT	204	213	205	
	# included in PP	168	164	169	
WA17823*	# of Patients Randomized	394	401	401	
	# included in ITT	393	399	398	
	# included in PP	338	347	359	
WA17824†	# of Patients Randomized	101		288	284
	# included in ITT	99		286	284
	# included in PP	92		265	259
WA18062*	# of Patients Randomized	161	164	174	
	# included in ITT	158	161	170	
	# included in PP	111	109	127	
WA18063**	# of Patients Randomized	415		805	
	# included in ITT	413		803	
	# included in PP	330		692	

* +MTX
 ** +DMARDs
 † Monotherapy

In Study WA17822, a total of 623 patients were recruited into the study between February 25, 2005 and March 21, 2006 across 73 centers in 17 countries. Of the 623 patients enrolled in the study, 204 were randomized to receive placebo+MTX, 214 to TCZ 4mg/kg + MTX and 205 to TCZ 8 mg/kg + MTX. One patient randomized to the TCZ 4mg/kg + MTX group did not receive any study treatment and was therefore withdrawn from the study and was not included in the ITT population (Table 6). A total of 118 patients entered the escape phase due to insufficient therapeutic response (i.e. failed to achieve >20% improvement in both SJC and TJC at week 16). Fifty (8%) patients withdrew prematurely from the initial therapy and an additional seven patients withdrew prematurely from the escape therapy. The reasons for withdrawal are summarized in Table 7. Note that patients who entered the escape phase due to insufficient therapeutic response were not classed as withdrawing from initial study treatment and are, therefore, not reflected in Table 7. For the analysis of the primary endpoint, patients who received escape therapy were considered as non-responders. Nonetheless, approximately 93% of patients in the placebo + MTX group and the TCZ 8 mg/kg + MTX group completed 24 weeks of treatment (initial and escape) compared with 87% of patients in the tocilizumab 4 mg/kg + MTX group.

Table 7: Patient Disposition (ITT Population) – Study WA17822

	Placebo +MTX N=204	TCZ4mg/kg +MTX N=213	TCZ8mg/kg +MTX N=205
Withdrawal from Initial Therapy	12 (6%)	25 (12%)	13 (6%)
Reason for Withdrawal (Initial)			
Adverse Events ^a	5 (2%)	14 (7%)	12 (6%)
Death	1 (<1%)	0	0
Insufficient Therapeutic Response	3 (1%)	2 (1%)	0
Other Protocol Violation	1 (<1%)	1 (<1%)	0
Refused Treatment ^b	2 (1%)	6 (3%)	1 (<1%)
Failure to Return	0	1 (<1%)	0
Other	0	1 (<1%)	0
Received Escape therapy	68 (33%)	31 (15%)	19 (9%)
Withdrawal from Escape therapy	3 (4%)	3 (10%)	1 (5%)
Reason for Withdrawal (Escape)			
Adverse Events ^a	2 (3%)	2 (6%)	0
Insufficient Therapeutic Response	1 (1%)	1 (3%)	0
Other	0	0	1 (5%)
Completed 24 weeks (including escape)	189 (93%)	186 (87%)	191 (93%)

^a includes intercurrent illness

^b includes 'did not co-operate' and 'withdrew consent'

In Study WA17823, a total of 1196 patients were enrolled into the study between January 11, 2005 and May 31, 2007 across 137 centers in 15 countries. Of the 1196 patients enrolled in the study, 394 were randomized to receive placebo+MTX, 401 to TCZ 4mg/kg + MTX and 401 to TCZ 8 mg/kg + MTX. Six patients (1 randomized to the placebo+MTX, 2 to TCZ 4mg/kg + MTX, and 3 to TCZ8 mg/kg +MTX group) did not receive any study treatment and were therefore withdrawn from the study and were not included in the ITT population. The ITT population therefore comprised a total of 1190 patients (393 placebo+MTX, 399 TCZ 4+MTX, and 398 TCZ8+MTX), see Table 6.

A total of 258 patients entered the escape phase due to insufficient therapeutic response (i.e. failed to achieve >20% improvement in both SJC and TJC at week 16). There were 83 (7%) patients who withdrew prematurely from the initial therapy and an additional 12 patients withdrew prematurely from the escape therapy. The reasons for withdrawal are summarized in Table 8. Note that patients who entered the escape phase due to insufficient therapeutic response were not classed as withdrawing from initial study treatment and are, therefore, not reflected in Table 8. For the analysis of the primary endpoint, patients who received escape therapy were considered as non-responders. Nonetheless, approximately 92% of patients in the placebo +MTX and TCZ + MTX groups completed 24 weeks of treatment (initial and escape).

Table 8: Patient Disposition (ITT Population) – Study WA17823

	Placebo +MTX N=393	TCZ4mg/kg +MTX N=399	TCZ8mg/kg +MTX N=398
Withdrawal from Initial Therapy	27 (7%)	24 (6%)	32 (8%)
Reason for Withdrawal (Initial)			
Adverse Events ^a	7 (2%)	15 (4%)	21 (5%)
Death	1 (<1%)	0	0
Insufficient Therapeutic Response	9 (2%)	1 (<1%)	1 (<1%)
Other Protocol Violation	1 (<1%)	0	0
Refused Treatment ^b	7 (2%)	7 (2%)	9 (2%)
Failure to Return	1 (<1%)	1 (<1%)	0
Other	1 (<1%)	0	1 (<1%)
Received Escape therapy	150 (38%)	67 (17%)	41 (10%)
Withdrawal from Escape therapy	9 (6%)	2 (3%)	1 (2%)
Reason for Withdrawal (Escape)			
Adverse Events ^a	4 (3%)	1 (1%)	1 (2%)
Insufficient Therapeutic Response	4 (3%)	1 (1%)	0
Refused Treatment	1 (1%)	0	0
Completed 24 weeks (including escape)	356 (91%)	373 (93%)	366 (92%)

^a includes intercurrent illness

^b includes 'did not co-operate' and 'withdrew consent'

In Study WA17824, a total of 673 patients were randomized into the study between July 26, 2005 and September 22, 2006 across 120 centers in 18 countries. Of the 673 patients enrolled in the study, 284 were randomized to receive MTX (comprising 192 patients in the main study and 92 patients in the placebo-controlled substudy), 288 patients were randomized to receive TCZ 8mg/kg (comprising 200 patients in the main study and 88 patients in the placebo-controlled substudy) and 101 patients were randomized to receive placebo for 8 weeks followed by TCZ 8 mg/kg for 16 weeks in the placebo-controlled substudy. According to the Applicant, a total of four patients (2 randomized to the TCZ 8mg/kg, and 2 to placebo/TCZ8mg/kg) were not included in the ITT population due to significant audit findings at the centers in which they were enrolled. The ITT population therefore comprised a total of 669 patients (284 MTX only, 286 TCZ 8 only and 99 placebo/TCZ8), see Table 6.

In the main study, a total of 392 patients were randomized to MTX or TCZ 8 mg/kg. Of these, 23 patients prematurely withdrew from the study (Table 9). Note that patients in the main study group were not eligible to receive escape therapy. Only patients participating in the placebo-controlled substudy who experienced insufficient therapeutic response (i.e. failed to achieve >20% improvement in both SJC and TJC) at any visit prior to (but not including) the Week 8 visit could receive escape therapy, if deemed necessary by the investigator. Of the 279 patients in the placebo-controlled study, 32 patients received escape therapy with open label TCZ 8mg/kg. There were 34 (12%) patients who withdrew prematurely from the initial therapy in this placebo-controlled substudy and an additional three patients who withdrew prematurely from the escape therapy. The reasons for withdrawal are summarized in Table 9. Note that patients who entered the escape phase due to insufficient therapeutic response were not classed as withdrawing from initial study treatment and are, therefore, not reflected in Table 9. For the analysis of the primary endpoint, patients who received escape therapy were considered as non-responders.

Nonetheless, the majority of patients enrolled in this study completed 24 weeks of observation (MTX group: 262 patients [92%]; tocilizumab group 268 patients [94%] and placebo/tocilizumab group: 82 patients [83%]).

Table 9: Patient Disposition (ITT Population) – Study WA17824

	Placebo/TCZ8mg/kg N=99	MTX only N=284	TCZ8mg/kg only N=286
Main Study		192 (68%)	200 (70%)
Withdrawal from main study		14 (7%)	9 (5%)
Reason for Withdrawal (Initial)			
Adverse Events ^a		6 (3%)	4 (2%)
Death		0	1 (1%)
Insufficient Therapeutic Response		2 (1%)	0
Other Protocol Violation		0	0
Refused Treatment ^b		5 (3%)	3 (2%)
Failure to Return		1 (1%)	1 (1%)
Other		0	0
Completed 24 weeks		178 (93%)	191 (96%)
Placebo-controlled Substudy	99 (100%)	92 (32%)	88 (31%)
Withdrawal from Initial Therapy	18 (18%)	8 (9%)	8 (9%)
Reason for Withdrawal (Initial)			
Adverse Events ^a	5 (5%)	0	4 (5%)
Death	0 (0)	2 (2%)	1 (1%)
Insufficient Therapeutic Response	3 (3%)	1 (1%)	1 (1%)
Other Protocol Violation	2 (2%)	0	0
Refused Treatment ^b	3 (3%)	3 (3%)	2 (2%)
Failure to Return	4 (4%)	2 (2%)	0
Other	1 (1%)	0	0
Received Escape therapy at week 8	14 (14%)	11 (12%)	7 (8%)
Withdrawal from Escape therapy	1 (7%)	0	2 (29%)
Reason for Withdrawal (Escape)			
Adverse Events ^a	0		1 (14%)
Insufficient Therapeutic Response	1 (7%)		0
Failed to Return	0		1 (14%)
Completed 24 weeks (including escape)	82 (83%)	84 (91%)	77 (88%)

^a includes intercurrent illness

^b includes 'did not co-operate' and 'withdrew consent'

In Study WA18062, a total of 499 patients were enrolled into the study between May 27, 2005 and April 18, 2007 across 128 centers in 13 countries. Of the 499 patients enrolled in the study, 161 were randomized to receive placebo+MTX, 164 to TCZ 4mg/kg + MTX and 174 to TCZ 8 mg/kg + MTX. One patient randomized to the placebo + MTX group was withdrawn from the study before receiving any study treatment due to a latex allergy and was therefore not included in the ITT population. Meanwhile, nine patients, all of whom were enrolled at Site 56980 were also excluded

from the ITT population due to significant audit findings¹ at the site. The ITT population therefore comprised a total of 489 patients (158 placebo+MTX, 161 TCZ 4+MTX, and 170 TCZ8+MTX), see Table 6.

A total of 114 patients entered the escape phase due to insufficient therapeutic response (i.e. failed to achieve >20% improvement in both SJC and TJC at week 16). Meanwhile, 76 (16%) patients withdrew prematurely from the initial therapy and an additional 4 patients withdrew prematurely from the escape therapy. The reasons for withdrawal are summarized in Table 10. Note that patients who entered the escape phase due to insufficient therapeutic response were not classed as withdrawing from initial study treatment and are, therefore, not reflected in Table 10. For the analysis of the primary endpoint, patients who received escape therapy were considered as non-responders. Nonetheless, approximately 80% of patients in the placebo +MTX, 84% in the TCZ 4 mg/kg + MTX group and 87% in the TCZ 8mg/kg +MTX groups completed 24 weeks of treatment (initial and escape).

Table 10: Patient Disposition (ITT Population) – Study WA18062

	Placebo +MTX N=158	TCZ4mg/kg +MTX N=161	TCZ8mg/kg +MTX N=170
Withdrawal from Initial Therapy	29 (18%)	24 (15%)	23 (14%)
Reason for Withdrawal (Initial)			
Adverse Events ^a	7 (4%)	10 (6%)	11 (6%)
Death	0	0	0
Insufficient Therapeutic Response	18 (11%)	5 (3%)	4 (2%)
Other Protocol Violation	0	3 (2%)	3 (2%)
Refused Treatment ^b	4 (3%)	2 (1%)	4 (2%)
Failure to Return	0	4 (2%)	1 (1%)
Other	0	0	0
Received Escape therapy	66 (42%)	30 (19%)	18 (11%)
Withdrawal from Escape therapy	3 (5%)	1 (3%)	0
Reason for Withdrawal (Escape)			
Adverse Events ^a	2 (3%)	0	0
Insufficient Therapeutic Response	1 (2%)	1 (3%)	0
Refused Treatment	0	0	0
Completed 24 weeks (including escape)	126 (80%)	136 (84%)	147 (87%)

^a includes intercurrent illness

^b includes 'did not co-operate' and 'withdrew consent'

In Study WA18063, a total of 1220 patients were enrolled into the study between March 24, 2005 and August 24, 2006 across 130 centers in 18 countries. Of the 1220 patients enrolled in the study, 415 were randomized to receive placebo+DMARDs, 805 to TCZ 8 mg/kg + DMARDs. Four patients (two randomized to the placebo + DMARDs group and two randomized to TCZ 8 mg/kg +DMARDs) were withdrawn from the study before receiving any study treatment and were not

¹ According to the Applicant, major findings of noncompliance were observed including lack of investigator oversight of study staff. Concerns with data integrity and the general lack of oversight led to the premature closure of the site.

included in the ITT population. The ITT population therefore comprised a total of 1216 patients (413 placebo+DMARDs and 803 TCZ8+DMARDs), see Table 6.

A total of 64 patients entered the escape phase due to insufficient therapeutic response (i.e. failed to achieve >20% improvement in both SJC and TJC at week 16). None of these patients prematurely withdrew from the escape therapy. Meanwhile, 93 (8%) patients withdrew prematurely from the initial therapy. The reasons for withdrawal are summarized in Table 11. Note that patients who entered the escape phase due to insufficient therapeutic response were not classed as withdrawing from initial study treatment and are, therefore, not reflected in Table 11. For the analysis of the primary endpoint, patients who received escape therapy were considered as non-responders. Nonetheless, approximately 90% of patients in the placebo +DMARDs and 94% in the TCZ 8 mg/kg + DMARDs groups completed 24 weeks of treatment (initial and escape).

Table 11: Patient Disposition (ITT Population) – Study WA18063

	Placebo +MTX N=413	TCZ8mg/kg +DMARDs N=803
Withdrawal from Initial Therapy	42 (10%)	51 (6%)
Reason for Withdrawal (Initial)		
Adverse Events ^a	7 (2%)	30 (4%)
Death	1 (0)	2 (0)
Insufficient Therapeutic Response	15 (4%)	3 (0)
Other Protocol Violation	3 (1%)	0
Refused Treatment ^b	12 (3%)	13 (2%)
Failure to Return	2 (0)	2 (0)
Other	2 (0)	1 (0)
Received Escape therapy	45 (11%)	19 (2%)
Completed 24 weeks (including escape)	371 (90%)	752 (94%)

^a includes intercurrent illness

^b includes 'did not co-operate' and 'withdrew consent'

Patient characteristics

In general, baseline demographic, baseline RA characteristics, and baseline ACR core set demographics were well balanced among the treatment groups within each of the five Phase 3 studies (see Appendix 3 to Appendix 7).

Most patients were female and the racial demography was predominantly white and non-Hispanic. The mean age across studies ranged from 51 to 54 years and most patients were non-smokers. Baseline demographic characteristics for the pooled DMARD inadequate responder population are presented in Table 20.

The following is a short summary of patient characteristics taken from the individual study reports.

In Study WA17822, the majority of patients were female (about 80%) and white (75%). The age range of the patients was 20 to 81 years and the mean age was 51 years. More than 80% of patients were non-smokers. The mean duration of RA was approximately 7.5 years (median was about 4.6 to 5.9

years). Mean DAS28 at baseline was 6.8. There were also higher proportion of RF+ patients in the tocilizumab 4 mg/kg + MTX and 8 mg/kg + MTX groups at baseline (78% and 83%, respectively) compared with the placebo + MTX group (71%). Mean MTX dose at baseline was 15 mg/week in all three treatment groups. An equal proportion of patients in each group (approximately 55%) were taking concomitant oral corticosteroids at baseline. Baseline ACR responder core set demographics were also well balanced, with patients in all three groups having similar mean scores for SJC, TJC, HAQ-DI, patient's assessment of global health, physician's assessment of global health and patient's assessment of pain and similar mean values for CRP and ESR.

In Study WA17823, the majority of patients were female (about 82%) and white (70%). The age range of the patients was 18 to 84 years and the mean age was 52 years. More than 80% of patients were non-smokers. The mean duration of RA was 9 years (median was about 6.4 to 7.5 years). Mean DAS28 at baseline was 6.5. About 80% of patients were RF positive at baseline. Mean MTX dose at baseline was 15 mg/week in all treatment groups. Baseline ACR responder core set demographics were also well balanced, with patients in all three groups having similar mean scores for SJC, TJC, HAQ-DI, patient's assessment of global health, physician's assessment of global health and patient's assessment of pain and similar mean values for CRP and ESR.

In Study WA17824, the majority of patients were female (about 80%) and white (70%). The age range of the patients was 18 to 83 years and the mean age was 51 years. Approximately 80% of patients were non-smokers. A significant proportion of patients were DMARD naïve (45% in the MTX group and 40% in the tocilizumab group), while approximately 66% in each treatment group were MTX naïve. The mean duration of RA was approximately 6.4 years (median was about 3.2 years). Mean DAS28 at baseline was 6.7. About 75% of patients were RF positive at baseline. An equal proportion of patients in each group (approximately 47%) were taking concomitant oral corticosteroids at baseline. Baseline ACR responder core set demographics were also well balanced, with patients in all three groups having similar mean scores for SJC, TJC, HAQ-DI, patient's assessment of global health, physician's assessment of global health and patient's assessment of pain and similar mean values for CRP and ESR.

In Study WA18062, the majority of patients were female (about 80%) and white (about 90%). The age range of the patients was 19 to 83 years and the mean age was 53 years. More than 70% of patients were non-smokers. Patients in the tocilizumab 8 mg/kg + MTX group had a longer mean (12.6 years) and median (9.3 years) duration of RA than patients in the other two treatment groups (11.0 and 9.3 years, respectively, in the tocilizumab 4 mg/kg + MTX group and 11.4 and 8.1 years, respectively, in the placebo + MTX group. In addition, more patients in the tocilizumab 8 mg/kg + MTX group had RA for ≥ 10 years (53% versus 47% tocilizumab 4 mg/kg + MTX group and 44% in the placebo + MTX group. Mean DAS28 at baseline was 6.8. More than 70% of patients were RF positive at baseline. Baseline ACR responder core set demographics except ESR and CRP were also well balanced, with patients in all three groups having similar mean scores. The placebo + MTX group had higher mean and median baseline ESR and CRP values than the tocilizumab 8 mg/kg + MTX and tocilizumab 4 mg/kg + MTX groups; however baseline DAS28 scores, which measures disease activity, were similar between the groups.

In Study WA18063, the majority of patients were female (about 81%) and white (72%). The age range of the patients was 18 to 89 years and the mean age was 53 years. About 83% of patients were non-smokers. The mean number of previous DMARDs or anti-TNFs was 1.6 and the median was 1.0 in both treatment groups. The mean duration of RA was approximately 10 years (median was about 7 years). Mean DAS28 at baseline was 6.7. About 75% of patients were RF positive at baseline. An equal proportion of patients in each group (approximately 55%) were taking concomitant oral corticosteroids at baseline. Baseline ACR responder core set demographics were also well balanced, with patients in all three groups having similar mean scores for SJC, TJC, HAQ-DI, patient's assessment of global health, physician's assessment of global health and patient's assessment of pain and similar mean values for CRP and ESR.

Exposure to Study Medication

In Study WA17822, the majority of patients (77% to 84% across the groups) received the planned six infusions of initial or escape therapy. For initial treatment, the majority of patients received four or more infusions (92% to 96% across the groups), although the proportion of patients who received all six infusions of initial treatment was higher in the tocilizumab 4 mg/kg + MTX and 8 mg/kg + MTX groups (64% and 70%, respectively) than in the placebo + MTX group (53%) due to the higher proportion of patients who entered the escape phase at week 16 in the placebo + MTX group. The median total patient years exposure to initial study treatment was 0.46 years in each group; however, mean total patient years exposure to initial study treatment was longer in the tocilizumab + MTX groups, particularly the 8 mg/kg + MTX group, compared with the placebo + MTX group due to the loss of more patients to escape therapy from the placebo + MTX group than from the tocilizumab + MTX groups.

In Study WA17823, more patients in the tocilizumab + MTX arms (61% and 69%) compared with the placebo + MTX arm (48%) received 6 infusions of initial treatment; this difference is accounted for by more patients in the placebo + MTX arm stopping initial therapy due to inadequate efficacy and receiving escape therapy. The median duration of exposure to initial study treatment was 0.46 years across all treatment arms although the mean duration was modestly longer in the tocilizumab + MTX arms compared with the placebo + MTX arm (0.39 yrs versus 0.42 yrs and 0.43 yrs). The sum of the individual patient years exposure to study treatment was longer in both tocilizumab + MTX arms (approximately 169 years) compared to the placebo + MTX arm (153 years), probably due to the fact that more patients in the placebo + MTX arm stopped initial treatment due to inadequate efficacy and entered the escape phase.

In Study WA17824, the majority of patients (82% in the MTX group and 83% in the tocilizumab group) received the planned six infusions of initial randomized therapy and at each infusion time point. Patient compliance with i.v. treatment was > 84% in the MTX and tocilizumab groups. In the placebo controlled substudy up to 24 weeks, the majority of patients (70%, 78% and 72% in the placebo/tocilizumab, MTX and tocilizumab groups respectively) also received the planned six infusions.

In the primary analysis group, the mean cumulative number of tablets was 142 (86% of the original total allocated oral treatment) in the MTX group and 141 (86% of the original total allocated oral treatment) in the tocilizumab group. In the placebo controlled substudy up to 24 weeks the mean cumulative number of tablets was 116.5 (71.1% of the original total allocated oral treatment) in the placebo/tocilizumab group, 135 (82% of the original total allocated oral treatment) in the MTX group and 136 (83% of the original total allocated oral treatment) in the tocilizumab group. The mean extent of exposure to IV trial treatment in this study was 0.43 years in the MTX group and 0.44 years in the tocilizumab group. The total patient years of exposure to treatment (period from the first infusion at baseline visit to the study visit 28 days after the last infusion) was higher in the tocilizumab group compared with the MTX group (126 years vs. 123 years in the MTX group). A similar trend was observed for extent of exposure to initial oral study treatment.

In Study WA18062, 70% to 77% of patients across the three treatment groups received six infusions of either the treatment to which they were initially randomized and/or escape therapy. For the initial treatment, the proportion of patients who received all six infusions of assigned treatment was higher in the tocilizumab 8 mg/kg + MTX and 4 mg/kg + MTX groups (67% and 53%, respectively) than in the placebo + MTX group (33%) due to the fact that more patients switched to escape therapy at the time of or after their fourth infusion. The median extent of exposure (in patient years) to initial

randomized study treatment was longer in the tocilizumab + MTX groups (0.46 patient years) compared with 0.31 patient years in the placebo + MTX group. Similarly, the mean extent of exposure (in patient years) to initial randomized study treatment was longer in the tocilizumab + MTX groups, particularly the 8 mg/kg + MTX group, compared with the placebo + MTX group. Total patient years of exposure to treatment (period from the first infusion at baseline visit to the study visit 28 days after the last infusion) was longer in the tocilizumab 8 mg/kg + MTX and tocilizumab 4 mg/kg + MTX groups, 71 patient years and 64 patient years, respectively, compared with 55 patient years in the placebo + MTX group.

In Study WA18063, the majority of patients in both groups received the planned six infusions in combination with either their initial baseline stable DMARDs or escape therapy. The median extent of exposure to initial study treatment was 0.46 years in each group. Mean extent of exposure to initial study treatment was also similar at 0.44 years in the tocilizumab 8 mg/kg + DMARDs group compared with 0.42 years in the placebo + DMARDs group; the difference due to a slightly higher rate of early withdrawal in the placebo + DMARDs group. As expected because of the 2:1 randomization ratio of the tocilizumab 8 mg/kg + DMARDs group to the placebo + DMARDs treatment group, the total patient years of exposure to treatment in the tocilizumab 8 mg/kg + DMARDs group was more than double that of the placebo + DMARDs group.

3.1.3 SUMMARY OF RESULTS

3.1.3.1 Evaluation of ACR Response in Controlled Studies

The primary efficacy analyses in all five studies were based on the proportion of patients with an ACR20 response at Week 24. For the four placebo-controlled studies (WA17822, WA17823, WA18062 and WA18063), the statistical hypotheses were based on a superiority comparison against the control (placebo + DMARD) in the proportion of patients with an ACR20 response at Week 24. Meanwhile, for Study WA17824, the statistical hypothesis was based on a non-inferiority comparison of the TCZ 8 mg/kg arm against MTX. In studies WA17822, WA17823 and WA18062, which have two TCZ treatment arms plus a control arm, a sequential testing procedure was produced for the primary endpoint so that the TCZ 8 mg/kg arm was first compared with the placebo arm, and only if this comparison resulted in a p-value of ≤ 0.05 was a comparison of the TCZ 4 mg/kg with placebo performed.

Before I present the results from the primary analysis in Studies WA17822, WA17823, WA18062, and WA18063, I will present the result of the non-inferiority study (Study WA17824).

The results under “primary analysis” and “robustness analysis” were taken from the Applicant’s study report. The primary analysis utilized the primary method of handling missing data (i.e. patients who did not have the required data at Week 24, withdrew from the study before Week 24, received escape therapy, or had received intra-articular injections of corticosteroid within the 8 weeks prior to their week 24 assessment were classed as non-responders). Meanwhile, ‘robustness’ analysis utilized the LOCF method of handling missing data. All the analyses were conducted on the ITT and PP population.

Aside from the “primary” and “robustness” analyses, two additional analyses to assess the robustness of the primary analysis were performed by me. One approach utilized the BOCF method of handling missing data in each of the components. Results from re-analysis of the raw data suggest that there

were some discrepancies in the derived SJC and TJC data so I re-calculated the ACR20 response by incorporating my derived SJC and TJC data. The results from these analyses were consistent with the Applicant's primary and robustness analyses.

Based on the per-protocol primary analysis, the proportion of ACR20 responders at Week 24 was 52% in the MTX group and 71% in the tocilizumab group (Table 12). Applying the extended Mantel-Haenszel approach, the calculated weighted difference in proportion, adjusting for site and disease duration, in ACR20 response at 24 weeks was 0.21 (95% CI 0.13 to 0.29). See Appendix 1 for more detail of the method. The lower limit of the CI was 0.13 which is well above the -0.12 non inferiority level. Thus, treatment with tocilizumab was considered non inferior to treatment with MTX. The results were similar when the intent-to-treat population was used or when robustness analysis was performed.

Table 12: ACR20 response at Week 24 (ITT Population) – Study WA17824

Population		TCZ 8mg/kg	MTX	Weighted difference	95% Confidence interval
Per-protocol		N=265	N=259		
	Primary Analysis	187 (71%)	135 (52%) *	0.21	(0.13, 0.29)
	Robustness Analysis	192 (73%)	143 (55%) *	0.20	(0.12, 0.29)
	Reviewer's (BOCF)	188 (71%)	136 (53%) *	0.21	(0.12, 0.29)
	Reviewer's (Fixing SJC/TJC)	189 (71%)	137 (53%) *	0.20	(0.12, 0.28)
ITT		N=286	N=284		
	Primary Analysis	200 (70%)	149 (53%) *	0.19	(0.11, 0.27)
	Robustness Analysis	206 (72%)	159 (56%) *	0.18	(0.10, 0.26)
	Reviewer's (BOCF)	201 (71%)	150 (53%) *	0.19	(0.11, 0.27)
	Reviewer's (Fixing SJC/TJC)	202 (71%)	151 (53%) *	0.19	(0.11, 0.27)

As tocilizumab monotherapy was shown to be at least non-inferior to MTX monotherapy in the primary analysis, further testing for superiority was conducted in Study WA17824. The results from this study, together with the four placebo-controlled studies are summarized in (Table 13) in terms of the primary endpoint.

In summary, there is evidence that there is significantly larger proportion of ACR20 responders among patients treated with either tocilizumab with background MTX (Studies WA17822, WA17823 and WA18062), and tocilizumab with background DMARD (Study WA18063) compared to placebo (with background MTX, or with background DMARD), regardless of the tocilizumab dose. There is also evidence that there is significantly larger proportion of ACR20 responders among patients treated with tocilizumab monotherapy compared to MTX alone (Study WA17824).

Table 13: ACR20 response at Week 24 (ITT Population)

Study		Placebo	TCZ4mg/kg	TCZ8mg/kg	MTX
WA17822§		N=204	N=213	N=205	
	Primary Analysis	54 (27%)	102 (48%) *	120 (59%) *	
	Robustness Analysis Reviewer's (BOCF)	54 (27%) 54 (27%)	112 (53%) * 104 (49%) *	123 (60%) * 121 (59%) *	
WA17823§		N=392	N=399	N=399	
	Primary Analysis	106 (27%)	202 (51%) *	224 (56%) *	
	Robustness Analysis Reviewer's (BOCF)	113 (29%) 109 (28%)	215 (54%) * 205 (51%) *	237 (60%) * 226 (57%) *	
	Reviewer's (Fixing SJC/TJC)	110 (28%)	199 (50%) *	225 (57%) *	
WA17824†	Per Protocol			N=265	N=259
	Primary Analysis			187 (71%) *	135 (52%)
	Robustness Analysis Reviewer's (BOCF)			192 (73%) * 188 (71%) *	143 (55%) 136 (53%)
	Reviewer's (Fixing SJC/TJC)			189 (71%) *	137 (53%)
	ITT			N=286	N=284
	Primary Analysis			200 (70%) *	149 (53%)
	Robustness Analysis Reviewer's (BOCF)			206 (72%) * 201 (70%) *	159 (56%) 150 (53%)
	Reviewer's (Fixing SJC/TJC)			202 (71%) *	151 (53%)
WA18062§		N=158	N=161	N=170	
	Primary Analysis	16 (10%)	49 (30%) *	85 (50%) *	
	Robustness Analysis Reviewer's (BOCF)	21 (13%) 18 (11%)	56 (35%) * 51 (31%) *	92 (54%) * 89 (51%) *	
	Reviewer's (Fixing SJC/TJC)	18 (11%)	50 (30%) *	91 (52%) *	
WA18063‡		N=415		N=804	
	Primary Analysis	101 (25%)		488 (61%) *	
	Robustness Analysis Reviewer's (BOCF)	108 (26%) 101 (24%)		510 (64%) * 490 (61%) *	
	Reviewer's (Fixing SJC/TJC)	102 (25%)		492 (61%) *	

† Monotherapy
 § +MTX
 ‡ +DMARDs
 * p<0.0001

Continuous responder curves for each treatment arm were plotted for the ACRn scores at week 24 in all four placebo-controlled studies and non-inferiority study (Figure 1 to Figure 5). ACRn is a specific percentage response achieved at Week 24 by a patient using the ACR response criteria. The derivation rule is described in Appendix 8.

Note that in these plots, all patients who drop out of the study are considered non-responders. These figures were created to provide a visual display of the relative benefit of various doses across the entire range of responses. The x-axis shows the percent ACR response achieved at week 24 (i.e. percentage improvement in disease activity), and the y-axis shows the corresponding percentage of patients achieving that level of response. The curves for the active arms were compared to placebo using the Kolmogorow-Smirnov test.

In all studies, there is a clear separation of curves between tocilizumab 4mg/kg and placebo, and between tocilizumab 8 mg/kg and placebo whether they were taken in combination with MTX or DMARDs. There is also a clear separation of curves between tocilizumab 8 mg/kg alone and MTX alone. There is also evidence that numerically higher proportion of patients taking tocilizumab 8 mg/kg in combination with background MTX achieved improvement in disease activity compared to those taking TCZ 4mg/kg in combination with background MTX.

Figure 1: Response Profile at Week 24 – Study WA17822

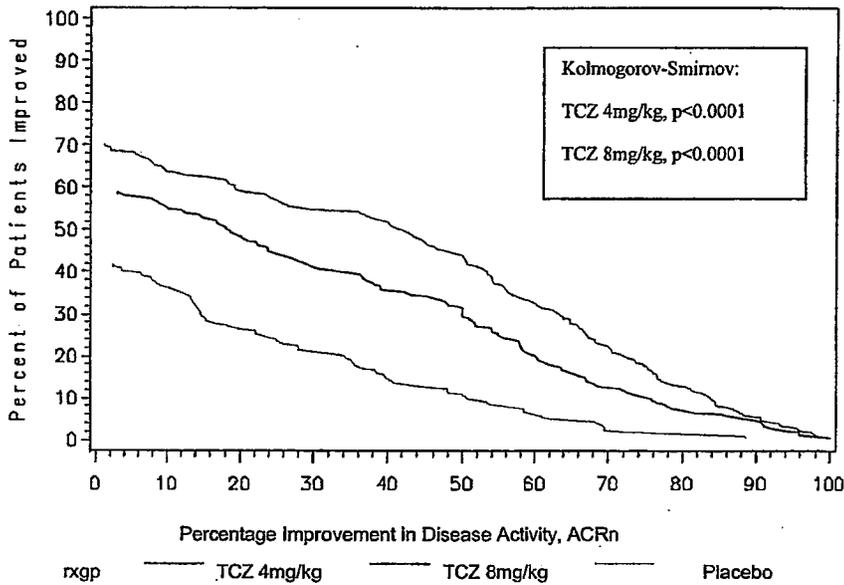


Figure 2: Response Profile at Week 24 – Study WA17823

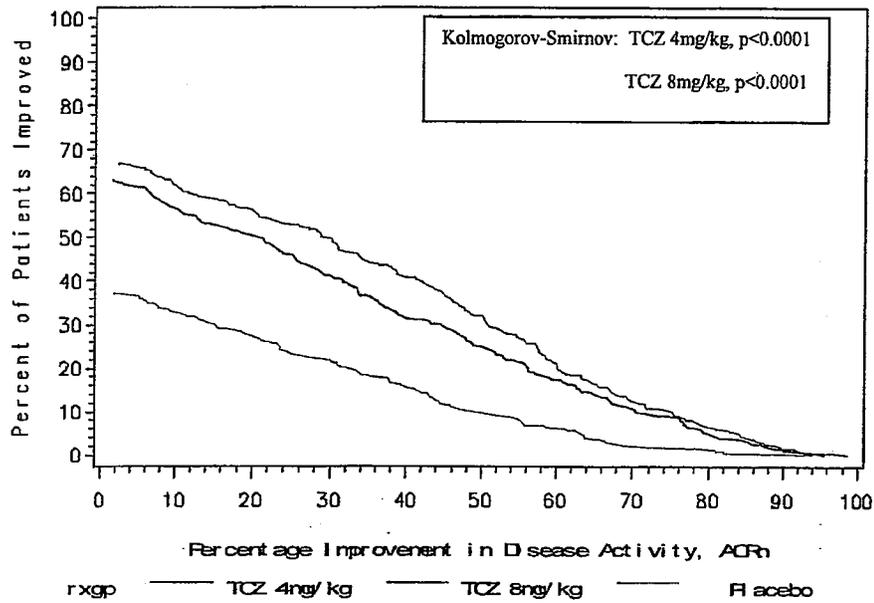


Figure 3: Response Profile at Week 24 – Study WA18062

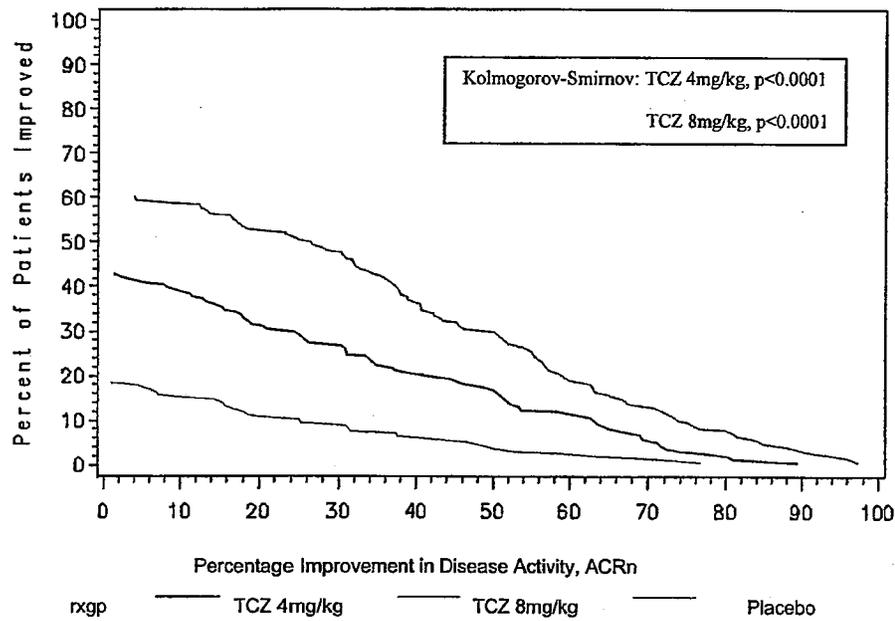


Figure 4: Response Profile at Week 24 – Study WA18063

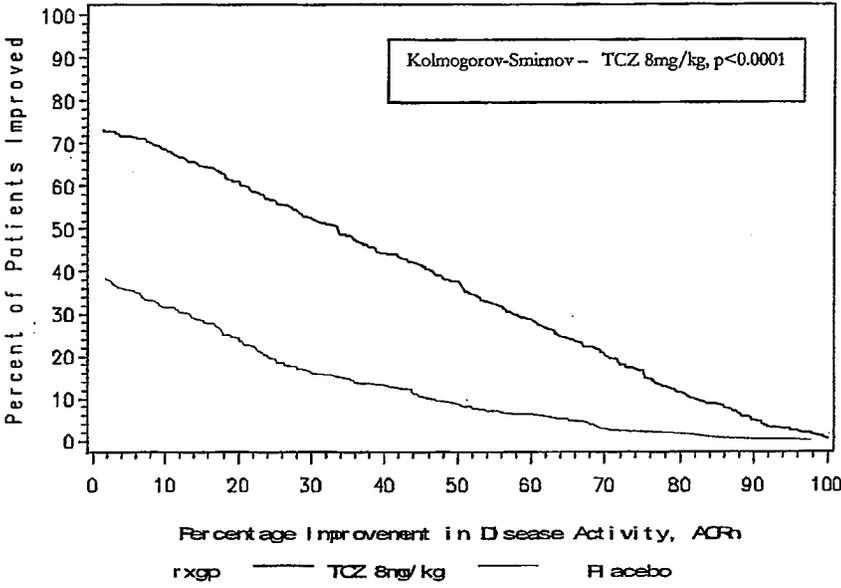
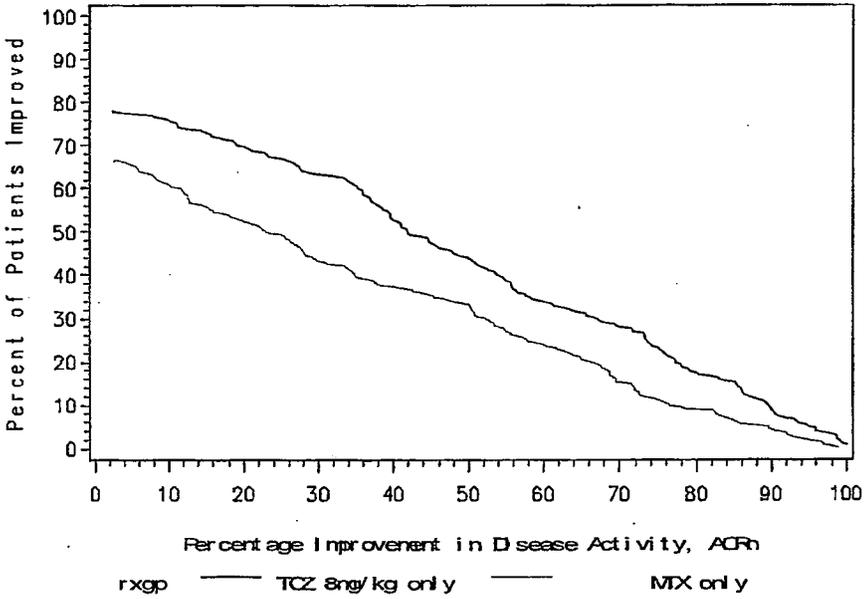


Figure 5: Response Profile at Week 24 – Study WA17824



To support the conclusions from the primary (non-inferiority) analysis in Study WA17824, a comparison was made between all patients treated with tocilizumab and the placebo treated patients enrolled into the placebo controlled substudy. The ITT and PP populations were used for this assessment. As patients in this study received placebo only for the first 8 weeks, this analysis compared proportions of patients achieving an ACR20 response at Week 8. The weighted difference in ACR20 response at 8 weeks was 0.43 (95% CI 0.34 to 0.52) in both the ITT and PP populations. Since the lower limit of the 95% CI for the weighted difference was greater than 0, tocilizumab 8 mg/kg is considered to be superior to treatment with placebo at Week 8. This result was statistically significant.

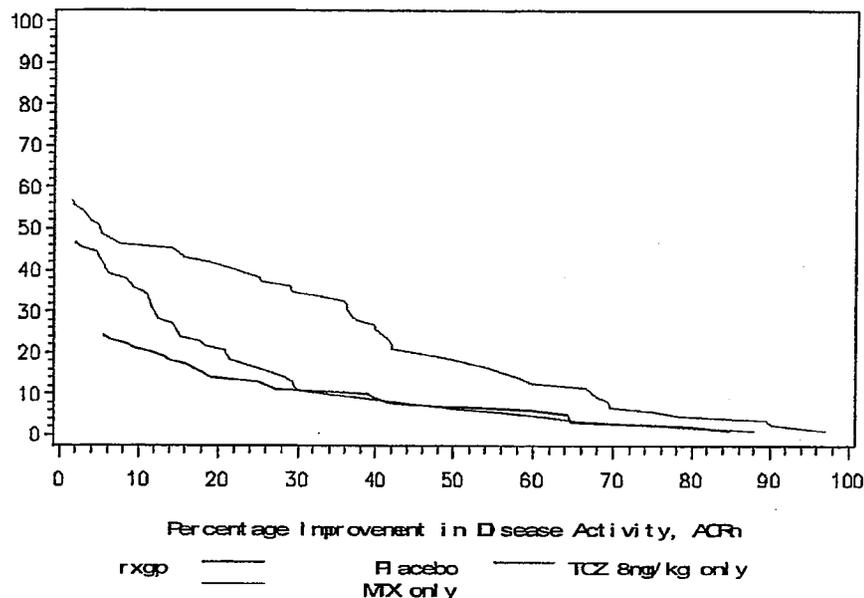
The Applicant conducted additional analysis with only those patients from the substudy using the ITT population. I also did an analysis using the PP population. The results were consistent with the full population, i.e. all tocilizumab patients (Table 14). Treatment with tocilizumab in patients enrolled into the placebo-controlled substudy was still shown to be superior to treatment with placebo at Week 8.

Table 14: ACR20 response at Week 8 Substudy (ITT Population) – Study WA17824

Population		TCZ 8mg/kg	Placebo	Weighted difference	95% Confidence interval
All tocilizumab	ITT Population	N=286 159 (56%)	N=99 13 (13%) *	0.43	(0.34, 0.52)
	PP Population	N=265 149 (56%)	N=92 13 (14%) *	0.43	(0.34, 0.52)
Placebo-controlled substudy	ITT Population	N=86 35 (41%)	N=99 13 (13%) *	0.28	(0.16, 0.40)
	PP Population	N=77 32 (42%)	N=92 13 (14%) *	0.28	(0.16, 0.40)

A plot of the response profile for this substudy is presented in Figure 6. Like the Week 24 plot, there is also a clear separation of curves between tocilizumab 8 mg/kg alone and MTX along at Week 8.

Figure 6: Response Profile at Week 8 (placebo-controlled substudy) – Study WA17824



The following are secondary endpoints that were examined by the Applicant and by me. This includes ACR50, ACR70, and the individual ACR components. Note that the results from the analyses of patient-reported outcomes (using the SF36 and FACIT-F questionnaires), patient's disease activity (DAS28), as well as the hemoglobin levels are not included in this review. After consulting with Dr. Okada, the results from the analyses of these endpoints, presented in the clinical section of the label, will be removed. Reader is referred to Dr. Okada's review for more detail of the rationale behind the decision to exclude these endpoints in the label.

ACR50 and ACR70 responses

There is evidence that the proportion of ACR50 (Table 15) and ACR70 (Table 16) responders at week 24 was also higher among patients treated with tocilizumab 4 mg/kg or 8 mg/kg compared to patients taking placebo (in combination with background MTX or DMARDs). Similarly, the proportion of ACR50 and ACR70 responders at week 24 was also higher among patients treated with tocilizumab 8 mg/kg monotherapy compared to MTX monotherapy.

Table 15: ACR50 response at Week 24 (ITT Population)

Study		Placebo	TCZ4mg/kg	TCZ8mg/kg	MTX
WA17822§	Primary Analysis	22 (11%)	67 (32%) *	90 (44%) *	
	Robustness Analysis	22 (11%)	70 (33%) *	92 (45%) *	
WA17823§	Primary Analysis	38 (10%)	100 (25%) *	128 (32%) *	
	Robustness Analysis	39 (10%)	104 (26%) *	135 (34%) *	
WA17824†	Primary Analysis (PP) Analysis (ITT)			115 (43%) * 126 (44%) *	85 (33%) 95 (34%)
WA18062§	Primary Analysis	6 (4%)	27 (17%) *	49 (29%) *	
	Robustness Analysis	7 (4%)	31 (19%) *	51 (30%) *	
WA18063‡	Primary Analysis	37 (9%)		302 (38%) *	
	Robustness Analysis	37 (9%)		313 (39%) *	

† Monotherapy
 § +MTX
 ‡ +DMARDs
 * p<0.0001

Table 16: ACR70 response at Week 24 (ITT Population)

Study		Placebo	TCZ4mg/kg	TCZ8mg/kg	MTX
WA17822§	Primary Analysis	4 (2%)	26 (12%) *	45 (22%) *	
	Robustness Analysis	4 (2%)	28 (13%) *	46 (22%) *	
WA17823§	Primary Analysis	8 (2%)	44 (11%) *	50 (13%) *	
	Robustness Analysis	8 (2%)	45 (11%) *	52 (13%) *	
WA17824†	Primary Analysis (PP) Analysis (ITT)			73 (28%) * 80 (28%) *	39 (15%) 43 (15%)
WA18062§	Primary Analysis	2 (1%)	8 (5%)	21 (12%) **	
	Robustness Analysis	2 (1%)	9 (6%)	22 (13%) **	
WA18063‡	Primary Analysis	12 (3%)		165 (21%) *	
	Robustness Analysis	12 (3%)		173 (22%) *	

† Monotherapy
 § +MTX
 ‡ +DMARDs
 * p<0.0001
 ** p<0.001

The proportion of patients with an ACR20 response at weeks 2, 4, 8, 12, 16, 20 and 24 are presented in Figure 7 to Figure 11. A summary of ACR20 response rates over time can be found in Appendix 9. Note that there is slight discrepancy between the Applicant's and my results and both are presented in Appendix 9.

Except in Study WA18062, a separation between the tocilizumab and placebo in ACR20 response rates was apparent at week 2. In study WA18062, the separation at week 2 was of a smaller magnitude than the other studies and is more apparent at week 4. Note that the ACR20 responses continued to increase over time before stabilizing at week 12 (Studies WA17822, WA17823, WA18062) and at week 16 (Study WA18063) or in some case, decreasing slightly at week 24, particularly in the 8 mg/kg + MTX group. Nonetheless, differences between the tocilizumab and placebo were maintained until week 24. At all time points after week 2, the greatest response rates were observed in the tocilizumab 8 mg/kg + MTX group (Studies WA17822, WA17823, and WA18062).

Figure 7: Proportion of ACR20 responders by week – Study WA17822 (Reviewer’s)

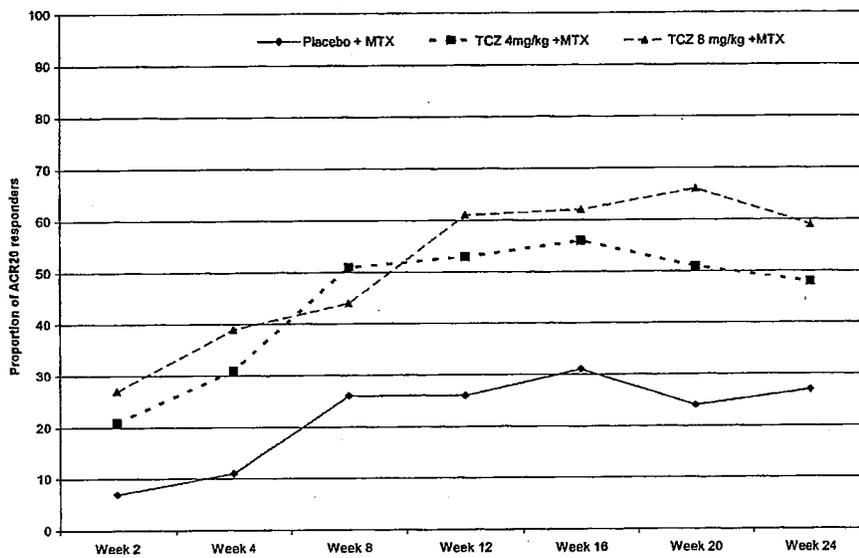


Figure 8: Proportion of ACR20 responders by week – Study WA17823 (Reviewer’s)

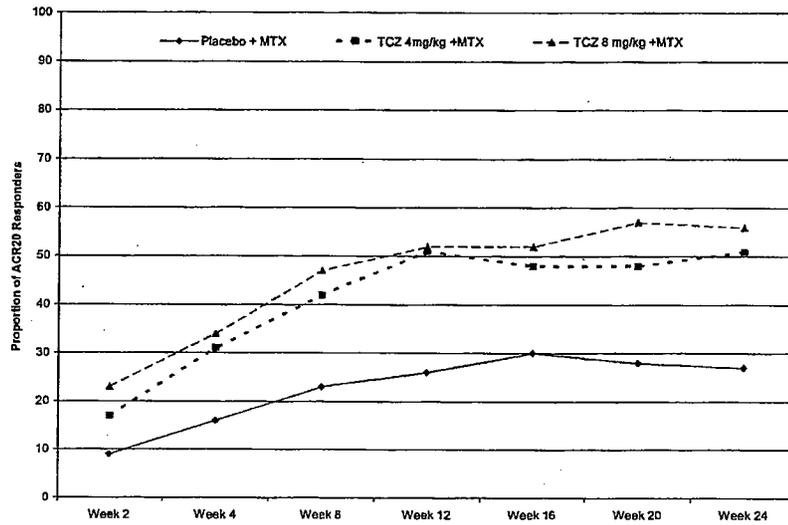


Figure 9: Proportion of ACR20 responders by week – Study WA18062 (Reviewer’s)

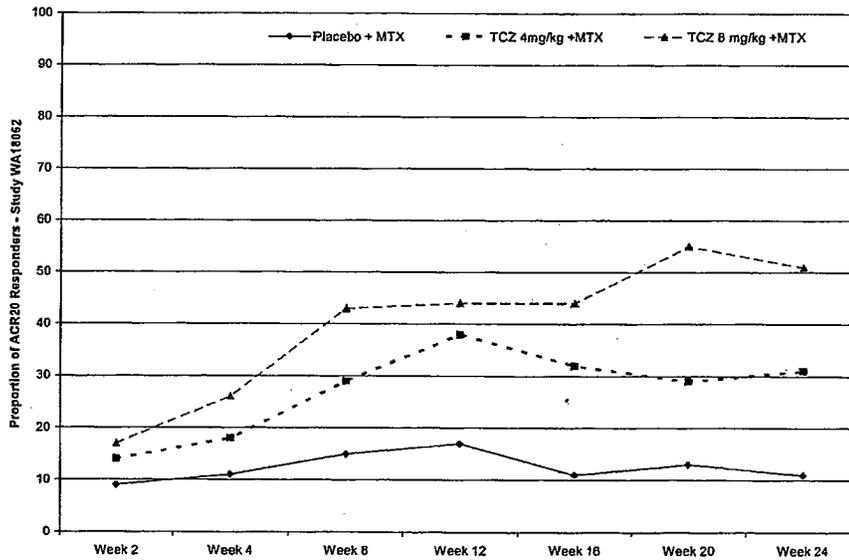


Figure 10: Proportion of ACR20 responders by week – Study WA18063 (Reviewer’s)

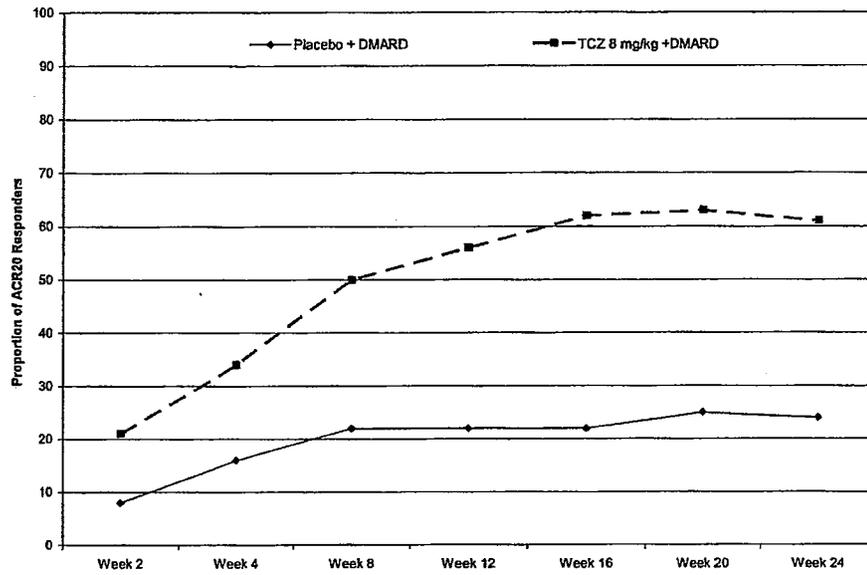
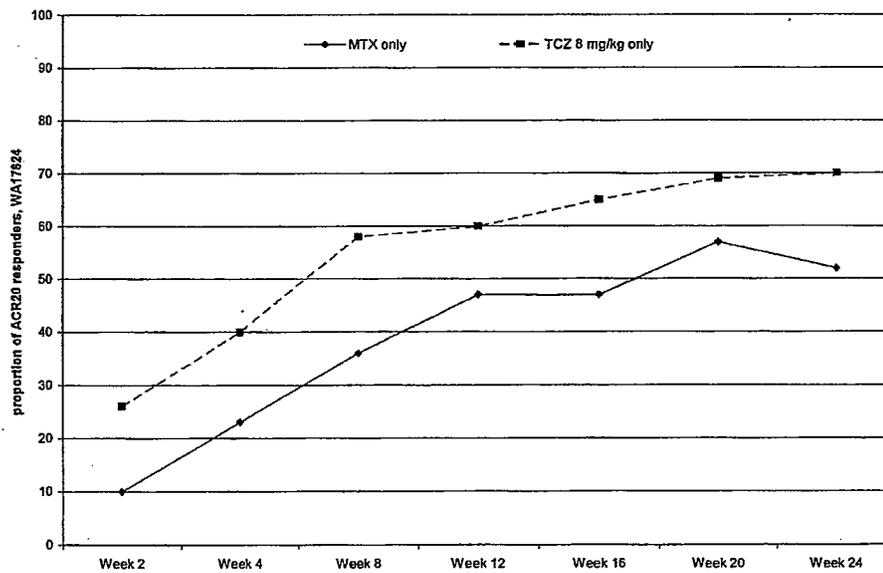


Figure 11: Proportion of ACR20 responders by week (ITT Population) – Study WA17824 (Reviewer’s)



Similar plots of ACR50 and ACR70 responses over time are presented in Figure 12 to Figure 16 and Figure 17 to Figure 21, respectively. Except in Study WA18062, there is clear separation in ACR50 responses between the tocilizumab and placebo groups beginning at week 4 (Studies WA17822, WA18063 and WA17824) and beginning at week 8 (Studies WA17823 and WA18062). In Study WA18062, it appears that the separation from placebo is evident in the 8 mg/kg + MTX group only. Like the ACR50 responses, there is still clear separation in ACR70 responses between the tocilizumab and placebo groups beginning at week 8 (except for the 4 mg/kg +MTX group in Study WA18062).

Like the ACR20, the greatest ACR50 and ACR70 response rates were observed in the tocilizumab 8 mg/kg + MTX group (Studies WA17822, WA17823, and WA18062). There is also evidence that ACR50 responses and ACR70 responses continued to increase over time, particularly in the 8 mg/kg tocilizumab group either as a monotherapy or in combination with MTX or DMARD.

Figure 12: Proportion of ACR50 responders by week – Study WA17822 (Reviewer's)

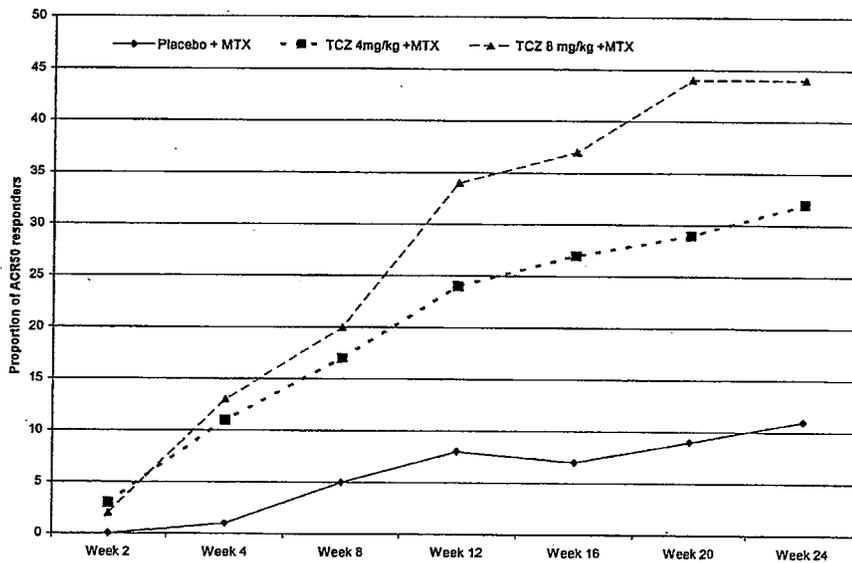


Figure 13: Proportion of ACR50 responders by week – Study WA17823 (Reviewer’s)

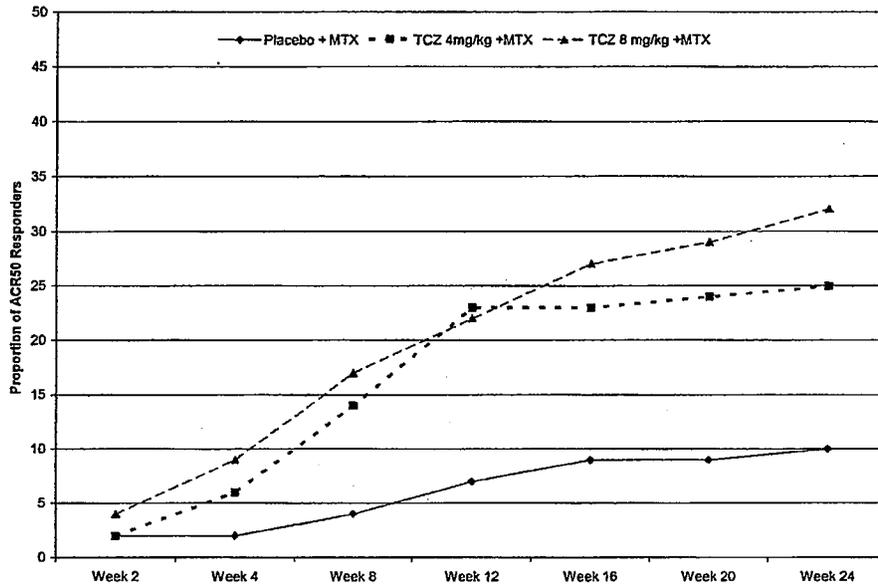


Figure 14: Proportion of ACR50 responders by week – Study WA18062 (Reviewer’s)

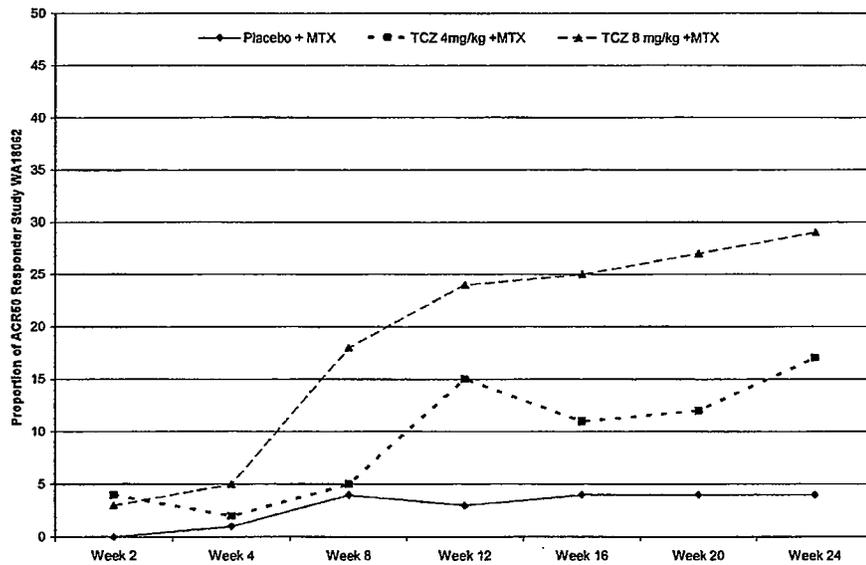


Figure 15: Proportion of ACR50 responders by week – Study WA18063 (Reviewer’s)

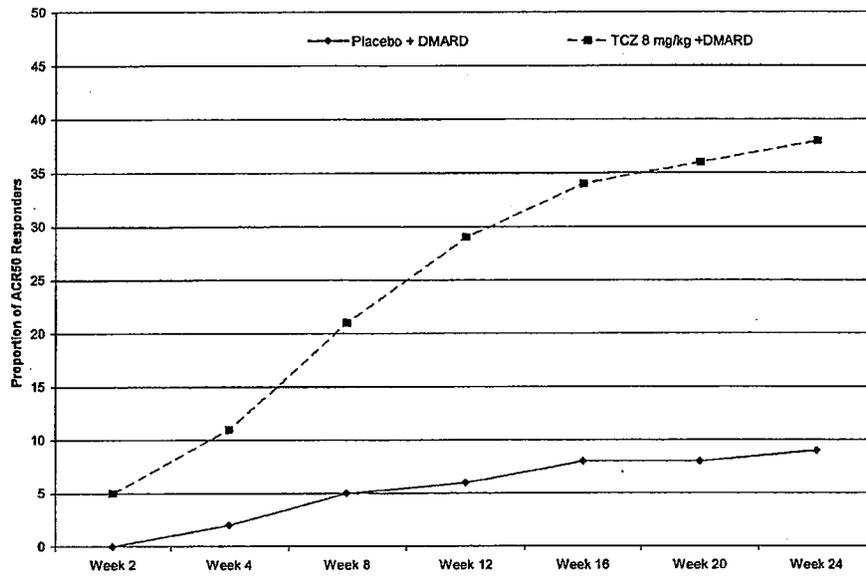


Figure 16: Proportion of ACR50 responders by week (ITT population) – Study WA17824 (Reviewer’s)

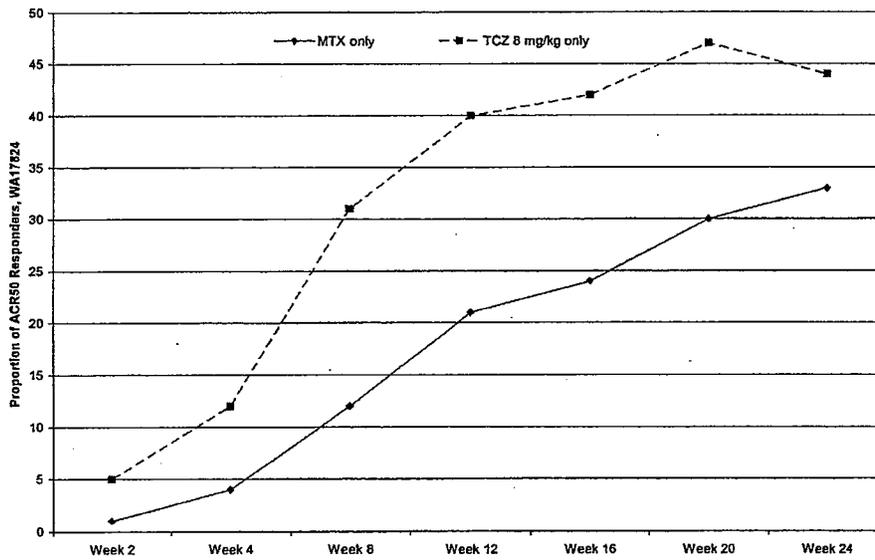


Figure 17: Proportion of ACR70 responders by week – Study WA17822 (Reviewer's)

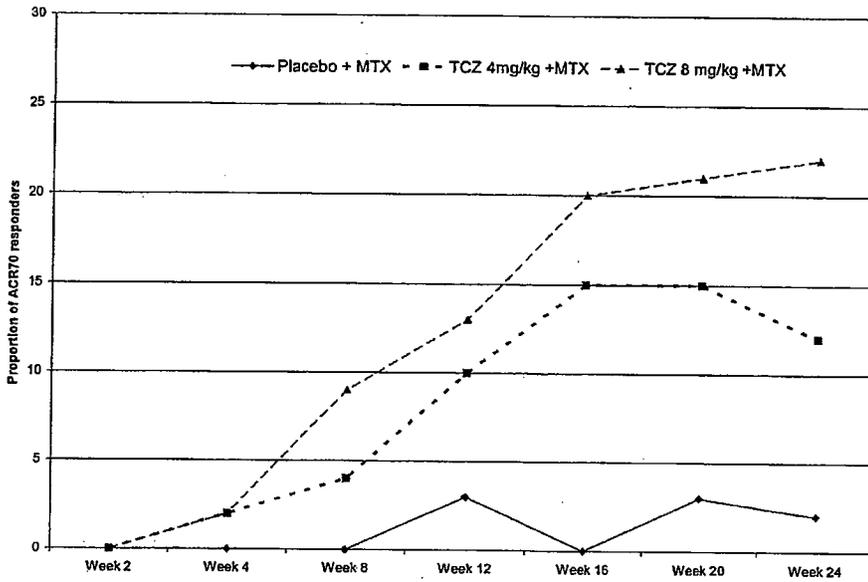


Figure 18: Proportion of ACR70 responders by week – Study WA17823 (Reviewer's)

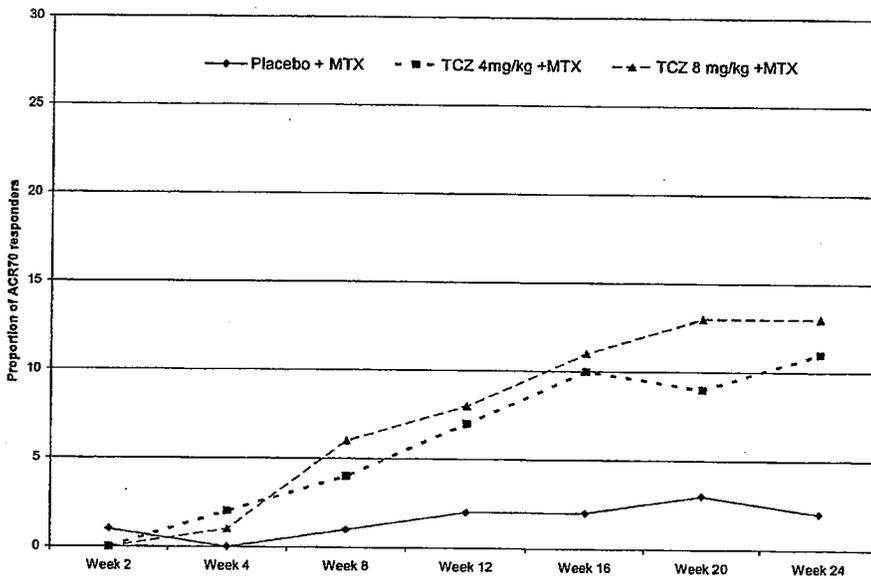


Figure 19: Proportion of ACR70 responders by week – Study WA18062 (Reviewer's)

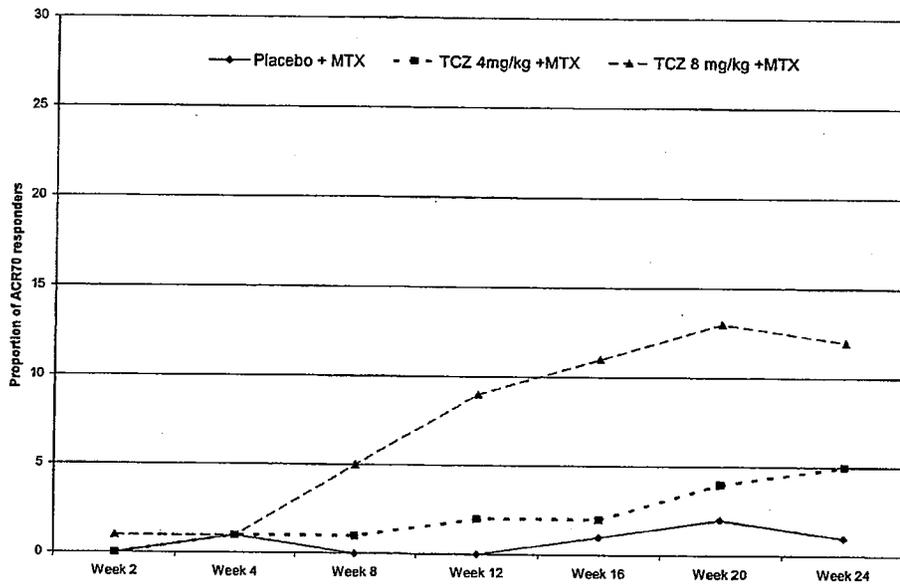


Figure 20: Proportion of ACR70 responders by week – Study WA18063 (Reviewer's)

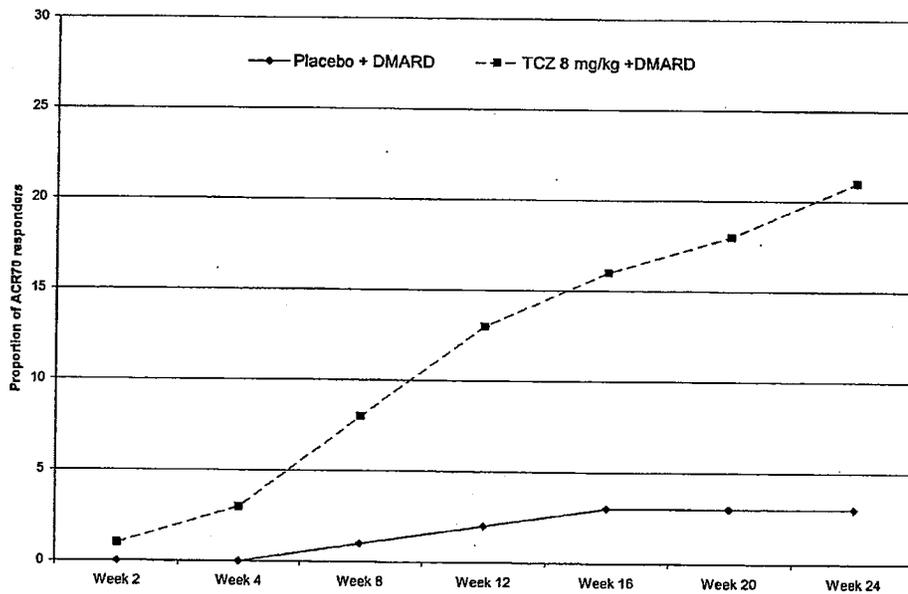
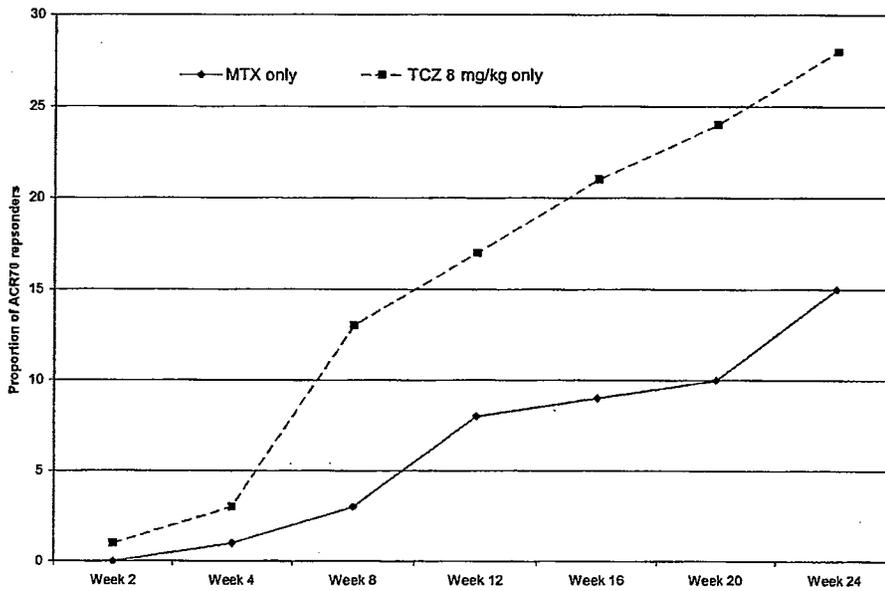


Figure 21: Proportion of ACR70 responders by week (ITT population) – Study WA17824 (Reviewer's)



The Applicant's summary of change from baseline values at Week 24 in the ACR core set parameters are provided on Appendix 10 to Appendix 14. For the primary analysis of ACR component scores, the Applicant applied LOCF for SJC and TJC components, while no imputation is used for the remaining components.

I conducted additional sensitivity analyses by applying LOCF and BOCF to missing data in all components. The results, although slightly different from the Applicant's did not alter the conclusion. Note that there were 106 patients in Study WA17822 and 71 patients in Study WA17823 that did not have baseline HAQ-DI score. The Applicant did not provide explanation for these missing scores. These patients were excluded from the analysis.

Superiority was tested for each of the individual ACR core set parameters using hierarchically ordered testing as described in Appendix 2. Except for Study WA17824, compared with placebo (with MTX or with DMARD), significant differences in the adjusted means were observed for all parameters in the tocilizumab 4 mg/kg (with MTX or with DMARD) group and the tocilizumab 8 mg/kg (with MTX or with DMARD) group, regardless of the imputation approach used.

In Study WA17824, large differences between MTX and tocilizumab were also observed for SJC, TJC, physicians global VAS, CRP, ESR and HAQ-DI. But because of the order of testing and because pain VAS did not show significant difference between the two treatment groups, none of the parameters after pain VAS can be tested for superiority. Consistent results were observed in the PP and the ITT populations.

Table 17: Change from Baseline in ACR Core Set Parameters at Week 24 (ITT) – Study WA17822

	Placebo + MTX N=204	TCZ 4 mg/kg +MTX N=213	TCZ 8 mg/kg + MTX N=205
SJC (LOCF) Mean (SD)	-5.8 (11.7)	-9.8 (11.5)**	-11.8 (11.5)**
TJC (LOCF) Mean (SD)	-7.6 (15.5)	-14.8 (17.0)**	-17.3 (15.5)**
LOCF			
Patient Global VAS	-10.4 (24.6)	-24.0 (26.1)**	-29.3 (28.8)**
Physician Global VAS	-18.0 (26.3)	-29.6 (26.7)**	-35.7 (22.9)**
Patient's Pain VAS	-7.3 (24.7)	-20.6 (25.6)**	-25.8 (27.1)**
CRP	-0.05 (3.3)	-1.5 (3.2)**	-2.3 (2.6)**
ESR	-6.7 (21.5)	-23.4 (27.2)**	-39.5 (25.3)**
HAQ-DI†	-0.2 (0.6)	-0.5 (0.6)**	-0.5 (0.6)**
BOCF			
Patient Global VAS	-10.7 (20.3)	-22.0 (25.8) **	-28.1 (28.5) **
Physician Global VAS	-18.9 (23.4)	-27.8 (25.7) **	-33.9 (23.8) **
Patient's Pain VAS	-8.1 (19.6)	-18.7 (24.3) **	-25.1 (26.4) **
CRP	-0.2 (2.1)	-1.2 (2.9) **	-2.0 (2.5) **
ESR	-4.8 (17.4)	-20.1 (26.4) **	-34.3 (26.9) **
HAQ-DI†	-0.2 (0.5)	-0.5 (0.7) *	-0.4 (0.5) **

HAQ-DI: 106 subjects did not have baseline measures (i.e. placebo 169, TCZ 4mg/kg+MTX 177, TCZ 8mg/kg+MTX 170)

*p<0.001

**p<0.0001

Table 18: Change from Baseline in ACR Core Set Parameters at Week 24 (ITT) – Study WA17823

	Placebo + MTX N=393	TCZ 4 mg/kg+MTX N=399	TCZ 8 mg/kg + MTX N=398
LOCF			
SJC	-3.3 (10.2)	-8.0 (9.2) **	-9.1 (9.6) **
TJC	-5.4 (14.1)	-12.4 (14.6) **	-14.2 (14.5) **
Patient Global VAS	-10.1 (26.1)	-21.8 (27.3)**	-22.4 (26.0)**
Physician Global VAS	-15.6 (26.3)	-30.6 (26.1)**	-34.9 (25.3)**
Patient's Pain VAS	-5.8 (24.8)	-16.8 (25.3)**	-19.2 (26.7)**
CRP	-0.1 (2.2)	-0.9 (2.4)**	-2.0 (2.5)**
ESR	-4.9 (24.1)	-20.6 (24.3)**	-35.4 (24.9)**
HAQ-DI†	-0.1 (0.5)	-0.4 (0.5)**	-0.4 (0.6)**
BOCF			
Patient Global VAS	-9.6 (21.6)	-19.6 (26.1) **	-20.8 (24.8) **
Physician Global VAS	-15.9 (23.1)	-28.3 (26.1) **	-32.4 (25.1) **
Patient's Pain VAS	-6.8 (19.5)	-15.2 (23.7) **	-17.8 (25.3) **
CRP	-0.2 (1.6)	-0.7 (2.1) *	-1.7 (2.5) **
ESR	-5.1 (18.5)	-17.2 (22.8) **	-30.1 (26.0) **
HAQ-DI†	-0.2 (0.4)	-0.4 (0.5) **	-0.4 (0.6) **

HAQ-DI: 71 subjects did not have baseline measures (i.e. placebo 368, TCZ 4mg/kg+MTX 376, TCZ 8mg/kg+MTX 375)

* p<0.001
 ** p<0.0001

Table 19: Change from Baseline in ACR Core Set Parameters at Week 24 (ITT) – Study WA18062

	Placebo + MTX N=158	TCZ 4 mg/kg + MTX N=161	TCZ 8 mg/kg + MTX N=170
SJC (LOCF) Mean (SD)	-1.6 (10.8)	-6.9 (10.9)**	-8.2 (12.1)**
TJC (LOCF) Mean (SD)	-1.1 (14.1)	-10.3 (14.4)**	-14.9 (17.1)**
LOCF			
Patient Global VAS	-8.2 (24.3)	-18.4 (30.3)*	-26.7 (30.5)***
Physician Global VAS	-9.6 (24.9)	-21.4 (25.3)**	-31.7 (26.8)***
Patient's Pain VAS	-5.3 (25.5)	-15.0 (28.0)*	-24.7 (29.3)***
CRP	-0.03 (3.7)	-1.1 (3.5)***	-2.2 (3.3)***
ESR	-3.0 (22.3)	-17.6 (25.8)***	-35.6 (28.8)***
HAQ-DI†	0.0 (0.4)	-0.2 (0.5)***	-0.3 (0.5)***
BOCF			
Patient Global VAS	-5.9 (19.8)	-16.6 (26.3) **	-25.9 (29.2) ***
Physician Global VAS	-9.0 (19.5)	-18.6 (24.2) **	-29.1 (26.2) ***
Patient's Pain VAS	-3.6 (20.3)	-13.3 (23.2) **	-24.7 (26.8) ***
CRP	-0.2 (2.3)	-0.9 (2.9) *	-1.9 (3.0) ***
ESR	-2.3 (11.9)	-13.2 (23.8) ***	-30.2 (29.9) ***
HAQ-DI†	-0.0 (0.2)	-0.2 (0.4) **	-0.3 (0.5) ***

HAQ-DI: 3 subjects did not have baseline measures (i.e. placebo + MTX 157, TCZ 4 mg/kg + MTX 159, TCZ 8mg/kg +MTX 170)

* p<0.05

** p<0.001

*** p<0.0001

Table 20: Change from Baseline in ACR Core Set Parameters at Week 24 (ITT) – Study WA18063

	Placebo + DMARD N=413	TCZ 8 mg/kg + DMARD N=803
LOCF		
SJC	-4.7 (10.5)	-10.3 (11.2) **
TJC	-8.7 (14.9)	-16.4 (15.3) **
Patient Global VAS	-12.1 (26.9)	-30.3 (29.9)**
Physician Global VAS	-17.5 (23.9)	-34.6 (24.3)**
Patient's Pain VAS	-8.7 (27.5)	-26.3 (29.4)**
CRP	-0.4 (2.5)	-2.3 (3.1)**
ESR	-4.8 (23.3)	-36.8 (26.4)**
HAQ-DI†	-0.1 (0.5)	-0.5 (0.6)**
BOCF		
Patient Global VAS	-11.6 (24.4)	-29.3 (29.4) **
Physician Global VAS	-16.6 (22.6)	-32.9 (24.9) **
Patient's Pain VAS	-8.6 (25.3)	-25.6 (28.7) **
CRP	-0.3 (2.1)	-2.1 (3.1) **
ESR	-5.1 (21.3)	-34.0 (27.5) **
HAQ-DI†	-0.2 (0.5)	-0.5 (0.6) **

HAQ-DI: 11 subjects did not have baseline measures (i.e. placebo + DMARD 411, TCZ 8mg/kg +DMARD 794)
 ** p<0.0001

Table 21: Change from Baseline in ACR Core Set Parameters at Week 24 (ITT) – Study WA17824

	PP		ITT	
	MTX only N=259	TCZ8mg/kg only N=265	MTX only N=284	TCZ8mg/kg only N=286
LOCF				
SJC	-8.7 (11.5)	-12.2 (11.0)***	-9.1 (11.5)	-12.1 (10.8)***
TJC	-15.2 (16.4)	-18.3 (15.5)*	-15.1 (16.6)	-18.0 (15.9)*
Patient Global VAS	-28.8 (30.2)	-32.8 (28.4)	-29.3 (30.1)	-33.1 (28.7)
Physician Global VAS	-28.8 (25.4)	-37.8 (23.4)***	-29.6 (25.3)	-37.5 (23.9)**
Patient's Pain VAS	-28.9 (28.9)	-30.8 (28.0)	-28.9 (29.0)	-30.6 (28.0)
CRP	-1.7 (3.3)	-2.5 (3.5)*	-1.8 (3.3)	-2.6 (3.5)*
ESR	-16.1 (25.7)	-34.6 (29.7)***	-16.6 (25.8)	-34.7 (29.8)***
HAQ-DI	-0.5 (0.6)	-0.7 (0.7)**	-0.5 (0.6)	-0.7 (0.7)*
BOCF				
Patient Global VAS	-27.4 (29.1)	-31.6 (28.5)	-27.5 (29.1)	-31.8 (28.9)
Physician Global VAS	-27.1 (25.0)	-36.8 (23.6)***	-27.4 (25.0)	-36.4 (24.0)***
Patient's Pain VAS	-27.4 (27.8)	-29.5 (27.6)	-27.2 (28.0)	-29.4 (27.6)
CRP	-1.6 (3.3)	-2.4 (3.3) *	-1.7 (3.2)	-2.4 (3.3)*
ESR	-14.8 (24.9)	-32.4 (30.6)***	-15.1 (24.8)	-32.0 (30.7)***
HAQ-DI	-0.5 (0.6)	-0.7 (0.7) **	-0.5 (0.6)	-0.7 (0.7)*

HAQ-DI: 3 subjects did not have baseline measures (i.e. placebo 98, TCZ 8mg/kg 285, MTX 283)

* p<0.01
 ** p<0.001
 *** p<0.0001

In collaboration with Dr. Okada, we explored the change from baseline in HAQ-DI score of patients. Responder was defined as patients who had at least 0.22 unit decrease in HAQ-DI score from baseline at the end of week 24. The objective was to determine whether there was difference in response rates between treatment groups. Missing data were imputed using LOCF and BOCF. These were post-hoc analyses with no adjustments for multiplicity.

There is a higher proportion of HAQ-DI responders among patients treated with either tocilizumab with background MTX (Studies WA17822, WA17823 and WA18062), or tocilizumab with background DMARD (Study WA18063) compared to patients treated with placebo (with background MTX, or with background DMARD), regardless of the tocilizumab dose (Table 22). There is also higher proportion of HAQ-DI responder among patients treated with tocilizumab monotherapy compared to MTX alone (Study WA17824).

Table 22: Responder Analysis of HAQ-DI at Week 24 (ITT)

Study		Placebo	TCZ4mg/kg	TCZ8mg/kg	MTX
WA17822§	Total	N=204	N=213	N=205	
	Baseline HAQ (N)	n=169	n=177	n=170	
	LOCF	72 (43%)	109 (62%)*	109 (64%)*	
	BOCF	58 (34%)	92 (52%)*	95 (56%)*	
WA17823§	Total	N=392	N=399	N=399	
	Baseline HAQ (N)	n=368	n=376	n=375	
	LOCF	153 (42%)	229 (61%)*	235 (63%)*	
	BOCF	112 (30%)	201 (53%)*	209 (56%)*	
WA17824†	Total			N=286	N=284
	Baseline HAQ (N)			n=285	n=283
	LOCF			213 (75%)**	188 (66%)
	BOCF			201 (71%)**	174 (61%)
WA18062§	Total	N=160	N=163	N=175	
	Baseline HAQ (N)	n=157	n=159	n=170	
	LOCF	34 (22%)	73 (46%)*	100 (59%)*	
	BOCF	21 (13%)	58 (36%)*	86 (51%)*	
WA18063‡	Total	N=415		N=804	
	Baseline HAQ (N)	n=411		n=794	
	LOCF	180 (44%)		526 (66%)*	
	BOCF	155 (38%)		499 (63%)*	

† Monotherapy
 § +MTX
 ‡ +DMARDs
 * p<0.001 (unadjusted)
 ** p<0.01 (unadjusted)

b(4)

The Applicant seeks a [redacted] based on the open-label extension studies (Studies WA18695 and WA18696). The extension studies WA18695/WA18696 were phase 3, open-label, international, multi-center studies in patients who had moderate to severe active RA at baseline in the core studies and completed 24 weeks of treatment in those studies (Figure 22). The studies, although identical, were assigned two separate protocol numbers for operational reasons. Protocol WA18695 was written for patients completing core study WA17822 and protocol WA18696 for patients completing one of the core studies WA18062, WA18063, WA17824, or WP18633. These two studies were conducted in order to continue treatment in patients who had completed a previous Phase 3 study (Studies WA18062, WA18063, WA17822, and WA17824) or the phase 1 patient study WP18663 and to assess the long-term safety and efficacy of 8 mg/kg tocilizumab. Study WA17823 was not included at that time because it is ongoing and remains blinded to the one and two year time points.

Figure 22: Overall Study Design of the Extension Studies

	Last dose in core study (placebo or tocilizumab)			Last dose in extension studies
Core Study (blinded)	WA18695/ WA18696 enrollment period	Open-label tocilizumab (MRA) treatment period (8 mg/kg iv every 4 weeks)		Follow-up
	Core study follow-up visits	Stable background therapy (MTX or other DMARD, see Section 2.2.5.1)	Background therapy optional (changes allowed, see Section 2.2.5.1)	
	≤ 12 weeks	48 weeks	≤ 216 weeks	12 weeks

Source: Clinical Study Report, WA18965wa18696, page 55

According to the Applicant, a total of 2715 patients completed one of the core studies WA17822, WA18062, WA17824, or WA18063. Of these 274 patients were not enrolled in the long-term extension studies because they either withdrew their consent, they failed to meet the inclusion/exclusion criteria, or for 101 of the WA17824 patients, their enrollment was deferred until completion of an optional blinded “transition phase” specified in core study protocol WA17824. However, according to my calculation, there were 2710 that completed one of the core studies. See Appendix 15 for the patient disposition.

In these studies, all eligible patients were assigned to treatment with 8 mg/kg tocilizumab and they were administered every 4 weeks on an outpatient basis. In exceptional cases, this time could be extended up to 6 hours, and the dose of 8 mg/kg could be modified for safety reasons at any scheduled visit following the first dose of 8 mg/kg. According to the Applicant,

Under certain circumstances, described below, a temporary treatment interruption and a dose reduction to 4 mg/kg was recommended. In case the dose was reduced to 4 mg/kg, treatment with tocilizumab could be continued as long as no further safety concerns arose, and as long as efficacy (patient’s SJC and TJC before dose reduction) was maintained. A return to the 8 mg/kg dose was recommended if deemed clinically feasible.

According to the Applicant, all but two of the 2441 patients enrolled in the extension studies received at least one infusion of study medication under protocol WA18695 or WA18696 and were thus included in the safety analysis (Table 23). Patient 64839/4450 (protocol WA18696) delayed the baseline infusion to a date later than 20 Apr 2007 (data cut) due to a safety concern, and patient

46636/3589 (protocol WA18695) experienced an SAE (myocardial infarction) and died prior to the scheduled baseline infusion. Thus, the safety population consisted of 2439 patients. Of these, 2262 patients were included in the ITT analysis. One hundred seventy-seven patients were excluded from the ITT population because they did not receive their first tocilizumab infusion within 12 weeks after their last infusion in the core studies. These patients composed the modified intent-to-treat population (mITT), and their efficacy parameters were analyzed separately.

Table 23: Summary of Analysis Population

stecll Summary of Analysis Populations by Trial Treatment (All Patients)
 Protocol(s): WA18695 WA18696
 Analysis: ALL PATIENTS Center: ALL CENTERS

	Pooled MRA
No. of Patients Randomized	2441
No. Included in INTENT-TO-TREAT	2262
No. Excluded from INTENT-TO-TREAT	179
Did not receive first [extension] infusion prior to or [within] 12 weeks after the last infusion in the core study	177
Did not receive study medication in either WA18695 or WA18696	2
No. Included in SAFETY	2439
No. Excluded from SAFETY	2
Did not receive study medication in either WA18695 or WA18696	2

Exclusions from the ITT population due to the first infusion in the extension study being greater than 12 weeks after the last infusion in the core study form the mITT population
 EC11 02AUG2007:16:20:40 (1 of 1)

Source: Clinical Study Report (Study WA18695/WA18696), page 89

Note that the results presented by the Applicant on the efficacy parameters (ACR20, ACR50, ACR70, and ACR90 response rates over time) are based on interim analyses (up until the date of cut-off, i.e. April 20, 2007). At the point of the interim analyses, the median duration in the studies was 41 weeks in the WA17824 study group, 52 weeks in the WA18062 group, and 61 weeks in the WA17822 and WA18063 group. According to the Applicant,

Since these studies were still ongoing at the time of writing of this report, and since patients were enrolled over an extended period, the number of patients who had completed a scheduled efficacy assessment decreased at later visits. Results at later time points should be interpreted with caution. For this reason, the efficacy tables and plots shown in the report body were censored at the point when fewer than 5% of patients of the overall study group population had completed the assessment. The uncensored data set is provided in the supporting data presentations.

Considering that these studies were ongoing and only a partial amount of information is available, it is difficult to assess whether patients who were ACR20 responder at Week 24 during the core studies (i.e. double-blind phase) maintained their responder status over a period of 18 months. Furthermore, it is also difficult to assess _____ when there is no assay sensitivity in the extension study or when there are no pre-defined criteria (e.g. at least X proportion of patients who respond consecutively) that would allow us to determine _____ of effect.

b(4)

3.1.3.2 Efficacy Conclusion

In summary, there is evidence that significantly larger proportion patients treated with either tocilizumab with background MTX (Studies WA17822, WA17823 and WA18062), or tocilizumab with background DMARD (Study WA18063) achieved ACR20 response compared to patients treated with placebo (with background MTX, or with background DMARD), regardless of the tocilizumab dose. There is also evidence that a significantly larger proportion of patients treated with tocilizumab monotherapy (Study WA17824) achieved ACR20 response compared to patients treated with MTX alone.

Based on the responder analyses graphs, there is a clear separation of curves between tocilizumab 4mg/kg and placebo, and between tocilizumab 8 mg/kg and placebo whether they were taken in combination with MTX or DMARDs. There is also a clear separation of curves between tocilizumab 8 mg/kg alone and MTX alone. There is also evidence that numerically higher proportion of patients taking tocilizumab 8 mg/kg in combination with background MTX achieved improvement in disease activity compared to those taking TCZ 4mg/kg in combination with background MTX.

Except in Study WA18062, a separation between the tocilizumab and placebo in ACR20 response rates is apparent at week 2. In study WA18062, the separation is most apparent at week 4. At all time points after week 2, the greatest response rates are observed in the tocilizumab 8 mg/kg + MTX group (Studies WA17822, WA17823, and WA18062).

In terms of secondary endpoints, superiority was tested for the ACR50 and ACR70 response at Week 24, as well as for each of the individual ACR core set parameters using hierarchically ordered testing described in Appendix 2. In all studies including Study WA17824, the proportion of ACR50 and ACR70 responders at week 24 are higher among patients treated with tocilizumab 4 mg/kg or 8 mg/kg compared to patients taking placebo (either as monotherapy or in combination with background MTX or DMARDs).

In all studies except Study WA17824, there is evidence that tocilizumab 4 mg/kg (with MTX or with DMARD) group and the tocilizumab 8 mg/kg (with MTX or with DMARD) group is associated with improvements in each of the ACR core components (i.e. SJC counts, TJC counts, VAS pain score, etc.) compared to placebo, regardless of the imputation approach used.

In Study WA17824, large differences between MTX and tocilizumab are also observed for SJC, TJC, physicians global VAS, CRP, ESR and HAQ-DI. But because of the order of testing and because pain VAS did not show significant differences between the two treatment groups, none of the parameters after pain VAS can be tested for superiority.

As part of the exploratory analysis, HAQ-DI responder analysis was conducted. Responder is defined as patients who had at least 0.22 unit decreased in HAQ-DI score from baseline at the end of week 24. A larger proportion of HAQ-DI responders among patients treated with either tocilizumab with background MTX (Studies WA17822, WA17823 and WA18062), or tocilizumab with background DMARD (Study WA18063) are observed in comparison to patients treated with placebo (with background MTX, or with background DMARD), regardless of the tocilizumab dose. In addition, there is also higher proportion of HAQ-DI responders among patients treated with tocilizumab monotherapy compared to MTX alone (Study WA17824).

Considering that the open-label extension studies were ongoing and only a partial amount of information is available, it is difficult to assess whether patients who were ACR20 responder at Week

24 during the core studies (i.e. double-blind phase) maintained their responder status over a period of 18 months. Therefore, there is not sufficient information at this time to evaluate the

3.2 EVALUATION OF SAFETY

Dr. Sarah Okada reviewed the safety of tocilizumab in detail. The reader is referred to Dr. Okada's review for information regarding the adverse event profile.

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

In all five studies, subgroup analyses were conducted with respect to gender, race, and age for the primary efficacy endpoint ACR20 in the ITT population. A descriptive summary of the primary endpoint by each subgroup is presented in Appendix 16 to Appendix 20. In addition to age, gender and race, other baseline characteristics were explored. This includes region (i.e. South America, North America, Europe and the rest of the world), baseline rheumatoid factor (i.e. positive or negative), baseline CRP, duration of RA disease, smoking history (i.e. tobacco usage), weight, and ethnicity (i.e. Hispanic versus non-Hispanic). A logistic regression model using region instead of site, each baseline characteristic, and each baseline-by-treatment interaction term was conducted to explore the relationship between the subgroups and treatment.

In Study WA17822, the treatment by region interaction in the primary endpoint analysis (i.e. ACR20) is significant at the 5% level ($p=0.0323$). After re-analysis of the data, the treatment by baseline rheumatoid factor is also found to be significant at the 10% level ($p=0.0680$). Note that the Applicant found treatment by baseline rheumatoid factor to be not significant ($p=0.1380$). None of the other baseline characteristics tested are found to have any interaction with the treatment group.

Table 24 below presents the adjusted odds ratios for ACR20 response for the tocilizumab + MTX versus placebo + MTX treatment comparisons by region and baseline rheumatoid factor. The results suggest an interaction between treatment and region, and between treatment and baseline rheumatoid factor. Although there is higher proportion of ACR20 responders in the tocilizumab group in all subgroups, the magnitude of the difference is noticeable. Patients from South America may have a higher placebo/MTX response, and a slightly higher response on tocilizumab 4 mg/kg +MTX compared to tocilizumab 8 mg/kg + MTX, as shown in proportion of responders in each group as well as the 95% confidence interval (Table 24). Similarly, it appears that the magnitude is greater in the RF positive arm compared to the RF negative arm.

In terms of secondary endpoints, ACR50 and ACR70, it appears that there is quantitative interaction between treatment and ethnicity, as well as between treatment and duration of RA disease, respectively. There is some evidence of a lower proportion of placebo ACR50 responders among non-Hispanic patients that may have led to a larger treatment difference with any of the tocilizumab arms (Table 25). In terms of disease duration, the Applicant explored the ACR70 response rates by treatment groups for a range of different cut-off values for disease duration. I present the result in a graphical format (Figure 23). There appears to be a shift in the proportion of ACR70 responders in the tocilizumab 4 mg/kg group when the disease duration is greater than 4 years. It appears that when a patient has RA for more than 4 years, tocilizumab 4 mg/kg is not differentiating from the

placebo. In contrast, when patient has RA for less than 4 years, both tocilizumab 4mg/kg and 8 mg/kg appears to have an effect compared to placebo (Table 26).

None on the other baseline characteristics tested are found to have any interaction with the treatment group in the secondary endpoints, ACR50 responder or ACR70 responder.

Table 24: Proportion of ACR20 responders at Week 24 by Treatment Group and by Region and Baseline Rheumatoid Factor – Study WA17822

ACR20		Placebo + MTX	TCZ 4 mg/kg+MTX	TCZ 8 mg/kg + MTX
Region	Overall % responder OR (95% CI)*	N=204 54 (27%)	N=213 102 (48%) 2.6 (1.7, 3.9)	N=205 120 (59%) 3.9 (2.6, 6.0)
	North America % responder OR (95% CI)*	n=18 3 (17%)	n=19 9 (47%) 4.5 (1.0, 20.8)	n=18 9 (50%) 5.0 (1.1, 23.5)
	Europe % responder OR (95% CI)*	n=98 25 (26%)	n=105 39 (37%) 1.7 (0.9, 3.2)	n=100 62 (62%) 4.8 (2.6, 8.7)
	South America % responder OR (95% CI)*	n=58 22 (38%)	n=61 38 (62%) 2.7 (1.3, 5.7)	n=56 30 (54%) 1.9 (0.9, 4.0)
	Rest of the World % responder OR (95% CI)*	n=30 4 (13%)	n=28 16 (57%) 8.7 (2.4, 31.5)	n=31 19 (61%) 10.3 (2.9, 36.9)
Rheumatoid Factor	Overall % responder OR (95% CI)*	N=204 54 (27%)	N=213 102 (48%) 2.6 (1.7, 3.9)	N=205 120 (59%) 3.9 (2.6, 6.0)
	Negative % responder OR (95% CI)*	n=60 15 (25%)	n=46 16 (35%) 1.6 (0.7, 3.7)	n=34 11 (32%) 1.4 (0.6, 3.6)
	Positive % responder OR (95% CI)*	n=142 38 (27%)	n=166 85 (51%) 2.9 (1.8, 4.6)	n=171 109 (64%) 4.8 (3.0, 7.8)

* Adjusted Odds Ratios for ACR20 Response at Week 24 for All Pairwise Treatment Comparisons by Region or Rheumatoid Factor (ITT Population)

Table 25: Proportion of ACR50 responders at Week 24 by Treatment Group and by Ethnicity – Study WA17822

ACR50		Placebo + MTX	TCZ 4 mg/kg+MTX	TCZ 8 mg/kg + MTX
Ethnicity	Overall % responder OR (95% CI)*	N=204 54 (27%)	N=213 102 (48%) 2.6 (1.7, 3.9)	N=205 120 (59%) 3.9 (2.6, 6.0)
	Hispanics % responder OR (95% CI)*	n=63 12 (19%)	n=68 25 (37%) 2.5 (1.1, 5.5)	n=62 25 (40%) 2.9 (1.3, 6.4)
	Non-Hispanics % responder OR (95% CI)*	n=138 10 (7%)	n=144 42 (29%) 5.3 (2.5, 11.0)	n=143 65 (45%) 10.7 (5.2, 22.0)

* Adjusted Odds Ratios for ACR50 Response at Week 24 for All Pairwise Treatment Comparisons by Ethnicity (ITT Population)

Figure 23: Proportion of ACR70 Responders by Disease Duration (Cumulative)– Study WA17822

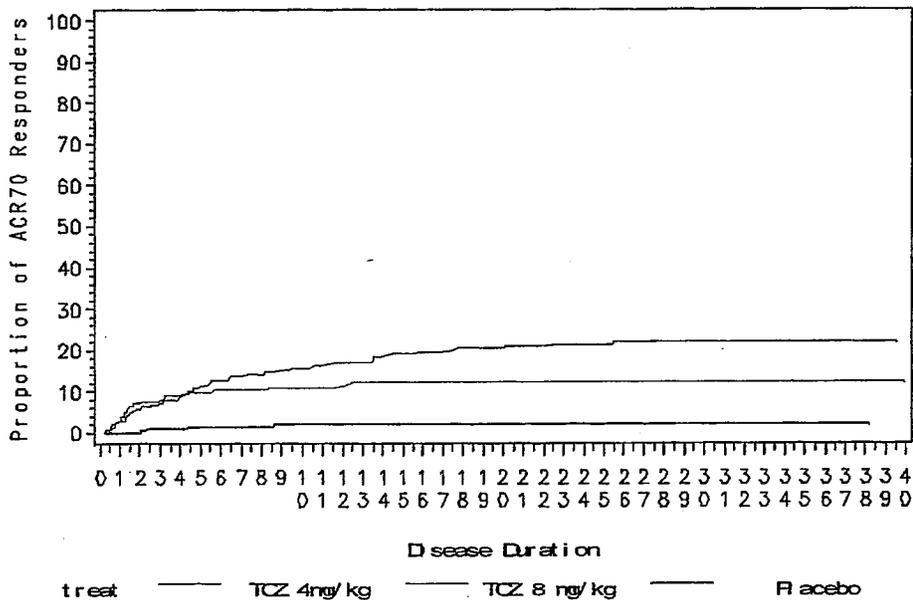


Table 26: Proportion of ACR70 responders at Week 24 by Treatment Group and by Duration of RA disease – Study WA17822

ACR70		Placebo + MTX	TCZ 4 mg/kg+MTX	TCZ 8 mg/kg + MTX
Duration of RA	Overall % responder OR (95% CI)*	N=204 54 (27%)	N=213 102 (48%) 2.6 (1.7, 3.9)	N=205 120 (59%) 3.9 (2.6, 6.0)
	≤ 4.2 years % responder OR (95% CI)*	n=65 2 (3%)	n=98 20 (20%) 8.3 (1.9, 37.1)	n=89 18 (20%) 8.0 (1.8, 36.2)
	> 4.2 years % responder OR (95% CI)*	n=139 2 (1%)	n=115 6 (5%) 3.7 (0.7, 18.8)	n=116 27 (23%) 21.2 (4.9, 91.7)

* Adjusted Odds Ratios for ACR70 Response at Week 24 for All Pairwise Treatment Comparisons by Duration of RA (ITT Population)
 Source: Clinical Study Report, page 5294

In Study WA18062, a treatment by ethnicity interaction in the primary endpoint analysis (i.e. ACR20) is found significant at the 10% level ($p = 0.0662$). Table 27 below presents the adjusted odds ratios for ACR20 response for the tocilizumab + MTX versus placebo + MTX treatment comparisons by ethnicity. Treatment effect in the non-Hispanic group is clear with higher proportion of ACR20 responders at both tocilizumab doses compared to placebo. In contrast, there appears to be no treatment difference in the Hispanic group. Because of the small numbers of Hispanic patients (i.e. 62 Hispanics versus 425 non-Hispanics), any claims in terms of patient's ethnicity are essentially unsupported.

None of the other baseline characteristics tested have any effect according to the primary endpoint analysis (i.e. ACR20 responder analysis), and to the secondary endpoints (i.e. ACR50 and ACR70).

Table 27: Proportion of ACR20 responders at Week 24 by Treatment Group and by Ethnicity – Study WA18062

ACR20		Placebo + MTX	TCZ 4 mg/kg+MTX	TCZ 8 mg/kg + MTX
Ethnicity	Overall % responder OR (95% CI)*	N=158 16 (10%)	N=161 49 (30%) 3.9 (2.1, 7.2)	N=170 85 (50%) 8.9 (4.9, 16.1)
	Hispanics % responder OR (95% CI)*	n=17 5 (29%)	n=22 6 (27%) 0.9 (0.2, 3.7)	n=23 12 (52%) 2.6 (0.7, 9.9)
	Non-Hispanics % responder OR (95% CI)*	n=140 11 (8%)	n=139 43 (31%) 5.3 (2.6, 10.7)	n=146 72 (49%) 11.4 (5.7, 22.9)

*Adjusted Odds Ratios for ACR50 Response at Week 24 for All Pairwise Treatment Comparisons by Region (ITT Population)

In patients treated with DMARDs (Study WA18063), the treatment by region interaction, treatment by race interaction, treatment by weight interaction, and treatment by baseline CRP in the primary endpoint analysis (i.e. ACR20) are found significant at the 5% level. None of the other baseline characteristics tested are found to have any interaction with the treatment group.

Table 28 below presents the adjusted odds ratios for ACR20 response for the tocilizumab + DMARD versus placebo + DMARD treatment comparisons by region and by race category. Like Study WA17822, there appears to be a quantitative interaction between treatment and region. It appears that the odds ratio seems to be higher in Europe than in North America. There also appears to be a quantitative interaction between treatment and race. Of note, the majority of patients in the study are 'white'; therefore, number of patients in the other race categories, such as blacks and 'other' are small. Thus, any claims of parity in terms of patient's race are essentially unsupported.

The baseline weight by treatment interaction is found to be significant at the 5% level ($p=0.0375$) for ACR20 responses. In order to assess the treatment effects within different weight categories, the Applicant categorized the weight into the following (prespecified in the Data Reporting and Analysis Manual): <60 kg, 60 kg to 100 kg and > 100 kg.

Table 29 presents the adjusted odds ratios for ACR20 response for the tocilizumab 8 mg/kg + DMARDs versus placebo +DMARDs groups in a comparison by each weight category. Although there is higher proportion of ACR20 responders in the tocilizumab group in each weight category compared to placebo, the magnitude of the difference is noticeable. It appears the odds ratio seems to be higher in patients with a weight of < 60 kg than in patients in the other weight categories.

Like baseline weight, baseline CRP value by treatment interaction is found to be significant at the 5% level ($p=0.0462$). In order to assess treatment effects within different baseline CRP categories, the Applicant categorized the baseline CRP into the following (prespecified in the Data Reporting and Analysis Manual): < 0.3, ≥ 0.3 to <1, ≥ 1 to < 3 and ≥ 3 to < 10 and ≥ 10 mg/dL. The interaction of these prespecified baseline CRP category variables is not found to be significant in the statistical model and no further investigation was performed.

In terms of secondary endpoint, ACR50, treatment by region and treatment by race are also found to be significant at the 10% level. Like the ACR20 subgroup analysis, there appears to be a quantitative interaction between treatment and region. It appears that the odds ratio seems to be higher in Europe than in North America. There also appears to be a quantitative interaction between treatment and race. Of note, the majority of patients in the study are 'white'; therefore, number of patients in the other race categories, such as blacks and 'other' are small. Thus, any claims of parity in terms of patient's race are essentially unsupported.

In terms of ACR70, there appears to be a quantitative interaction between treatment and baseline rheumatoid factor. It appears that the odds ratio seems to be higher in RF positive patients than in RF negative patients (Table 31).

None on the other baseline characteristics tested are found to have any interaction with the treatment group in the secondary endpoints, ACR50 responder or ACR70 responder.

Table 28: Proportion of ACR20 responders at Week 24 by Treatment Group and by Region and Race – Study WA18063

ACR20		Placebo + DMARD	TCZ 8 mg/kg + DMARD
Region	Overall % responder OR (95% CI)*	N=413 101 (24%)	N=803 488 (61%) 4.8 (3.7, 6.2)
	North America % responder OR (95% CI)*	n=182 44 (24%)	n=357 180 (50%) 3.2 (2.1, 4.7)
	Europe % responder OR (95% CI)*	n=107 18 (17%)	n=189 125 (66%) 9.7 (5.4, 17.4)
	South America % responder OR (95% CI)*	n=81 31 (38%)	n=171 130 (76%) 5.1 (2.9, 9.0)
	Rest of the World % responder OR (95% CI)*	n=43 8 (19%)	n=86 53 (62%) 7.0 (2.9, 17.0)
	Race	Overall % responder OR (95% CI)*	N=413 101 (24%)
White % responder OR (95% CI)*		n=297 66 (22%)	n=580 351 (61%) 5.4 (3.9, 7.4)
Black % responder OR (95% CI)*		n=27 6 (22%)	n=36 17 (47%) 3.1 (1.0, 9.6)
American Indian or Alaska % responder OR (95% CI)*		n=35 13 (37%)	n=84 62 (74%) 4.8 (2.1, 11.1)
Asian % responder OR (95% CI)*		n=41 9 (22%)	n=76 47 (62%) 5.8 (2.4, 13.8)
Other % responder OR (95% CI)*		n=13 7 (54%)	n=27 11 (41%) 0.6 (0.2, 2.2)

* Adjusted Odds Ratios for ACR20 Response at Week 24 for All Pairwise Treatment Comparisons by Region or Race (ITT Population)

Table 29: Proportion of ACR20 responders at Week 24 by Treatment Group and Weight Category – Study WA18063

ACR20		Placebo + DMARD	TCZ 8 mg/kg+DMARD
Weight	Overall	N=413	N=803
	% responder	101 (24%)	488 (61%)
	OR (95% CI)*		4.8 (3.7, 6.2)
	< 60 kg	n=98	n=179
% responder	17 (17%)	123 (69%)	
OR (95% CI)*		10.9 (5.9, 20.0)	
60 – 100 kg	n=281	n=555	
% responder	76 (27%)	327 (59%)	
OR (95% CI)*		3.9 (2.9, 5.3)	
> 100 kg	n=34	n=69	
% responder	8 (24%)	38 (55%)	
OR (95% CI)*		4.0 (1.6, 10.0)	

*Adjusted Odds Ratios for ACR50 Response at Week 24 for All Pairwise Treatment Comparisons by Weight (ITT Population)

Table 30: Proportion of ACR50 responders at Week 24 by Treatment Group and by Region and Race— Study WA18063

		Placebo +DMARD	TCZ 8 mg/kg + DMARD
ACR50: Region	Overall % responder OR (95% CI)*	N=413 37 (9%)	N=803 302 (38%) 3.9 (2.6, 6.0)
	North America % responder OR (95% CI)*	n=182 17 (9%)	n=357 108 (30%) 4.2 (2.4, 7.3)
	Europe % responder OR (95% CI)*	n=107 4 (4%)	n=189 79 (42%) 18.5 (6.5, 52.3)
	South America % responder OR (95% CI)*	n=81 11 (14%)	n=171 87 (51%) 6.6 (3.3, 13.3)
	Rest of the World % responder OR (95% CI)*	n=43 5 (12%)	n=86 28 (33%) 3.7 (1.3, 10.3)
Race	Overall % responder OR (95% CI)*	N=413 37 (9%)	N=803 302 (38%) 3.9 (2.6, 6.0)
	White % responder OR (95% CI)*	n=297 19 (6%)	n=580 221 (38%) 9.0 (5.5, 14.8)
	Black % responder OR (95% CI)*	n=27 4 (15%)	n=36 8 (22%) 1.6 (0.4, 6.2)
	American Indian or Alaska % responder OR (95% CI)*	n=35 7 (20%)	n=84 42 (50%) 4.0 (1.6, 10.2)
	Asian % responder OR (95% CI)*	n=41 5 (12%)	n=76 25 (33%) 3.5 (1.2, 10.1)
	Other % responder OR (95% CI)*	n=13 2 (15%)	n=27 6 (22%) 1.6 (0.3, 9.1)

* Adjusted Odds Ratios for ACR20 Response at Week 24 for All Pairwise Treatment Comparisons by Region or Race (ITT Population)

Table 31: Proportion of ACR70 responders at Week 24 by Treatment Group and by Baseline Rheumatoid Factor – Study WA18063

		Placebo +DMARD	TCZ 8 mg/kg + DMARD
ACR70: Rheumatoid Factor	Overall	N=413	N=803
	% responder	12 (3%)	165 (21%)
	OR (95% CI)*		8.6 (4.7, 15.7)
	Negative	n=102	n=179
	% responder	7 (9%)	31 (17%)
	OR (95% CI)*		2.8 (1.2, 6.7)
	Positive	n=311	n=624
	% responder	5 (2%)	134 (21%)
	OR (95% CI)*		16.7 (6.8, 41.3)

* Adjusted Odds Ratios for ACR20 Response at Week 24 for All Pairwise Treatment Comparisons by Rheumatoid Factor (ITT Population)

In Studies WA17823 and WA17824, none of the baseline characteristics tested has any effect based on the primary endpoint analysis (i.e. ACR20 responder analysis), as well as to the secondary endpoints ACR50 responder and ACR70 responder.

In conclusion, there is no consistent evidence of treatment by subgroup interaction across the five studies. It appears that 'region' may have an effect on treatment group differences, but so far, this is only evident in one MTX combination study (Study WA17822) and one DMARD combination study (Study WA18063). However, according to Dr. Okada, this finding is consistent with the other biologic products approved for the same indication. Furthermore, because the effect in North America remains positive and consistent with the overall conclusion, the regional differences are less worrisome.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

I did not identify any statistical issues in the BLA submission that could not be resolved by recoding and re-analyzing the data. For example, I identified various discrepancies between the raw and derived datasets. Reasons for most of these discrepancies were found not to affect the overall conclusion.

The primary objective in all five studies was to assess the efficacy of tocilizumab versus placebo in patients with moderate to severe active RA with regard to reduction in signs and symptoms over 6 months of treatment in combination with background MTX therapy (Studies WA17822, WA17823, and WA18062), or in combination with DMARD therapy (Study WA18063), as well as to assess the efficacy of TCZ monotherapy vs. MTX in patients who had not been treated with MTX within 6 months prior to randomization and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response (as determined by the investigator). The primary efficacy endpoint of all five studies was the proportion of ACR20 responders at week 24.

The primary endpoint was met in all five pivotal clinical studies (Table 13), and in the direct comparison between tocilizumab 8 mg/kg monotherapy and MTX dose escalated to 20 mg/wk within 8 weeks, tocilizumab efficacy was also shown to be different to that of MTX. There is also consistent evidence that tocilizumab 4 mg/kg in combination with MTX therapy is different to that of the placebo + MTX therapy; however, there is also evidence that numerically higher proportion of patients taking tocilizumab 8 mg/kg in combination with background MTX achieved improvement in disease activity compared to those taking TCZ 4mg/kg in combination with background MTX.

Higher proportion of patients taking tocilizumab also achieved ACR50 or ACR70 responder status compared to the placebo with combination therapy or MTX monotherapy in the various patient populations studied. Changes from baseline for each of the ACR core set parameters are also consistent with the composite scores

Except in Study WA18062, a separation between the tocilizumab combination therapy and monotherapy groups and the comparator groups in ACR20 response rates is apparent at week 2. In study WA18062, the separation is most apparent at week 4. At all time points after week 2, the greatest response rates are observed in the tocilizumab 8 mg/kg + MTX group (Studies WA17822, WA17823, and WA18062).

As part of the exploratory analysis, HAQ-DI responder analysis was conducted. Responder is defined as patients who had at least 0.22 unit decrease in HAQ-DI score from baseline at the end of week 24. A larger proportion of HAQ-DI responders among patients treated with either tocilizumab with background MTX (Studies WA17822, WA17823 and WA18062), and tocilizumab with background DMARD (Study WA18063) are observed in comparison to patients treated with placebo (with background MTX, or with background DMARD), regardless of the tocilizumab dose. In addition, there is also higher proportion of HAQ-DI responder among patients treated with tocilizumab monotherapy compared to MTX alone (Study WA17824).

Considering that the open-label extension studies were ongoing and only a partial amount of information was available, it is difficult to assess whether patients who are ACR20 responder at Week

24 during the core studies (i.e. double-blind phase) maintained their responder status over a period of 18 months. Therefore, there is not sufficient information at this time to evaluate the _____

b(4)

In terms of treatment by subgroup analysis, there was no consistent evidence of treatment by subgroup interaction across the five studies. It appeared that 'region' may have an effect on treatment group differences, but so far, this was only evident in one MTX combination study (Study WA17822) and one DMARD combination study (Study WA18063). However, according to Dr. Okada, this finding was consistent with the other biologic products approved for the same indication. Furthermore, because the effect in North America remained positive and consistent with the overall conclusion, the regional differences were less worrisome.

5.2 CONCLUSIONS AND RECOMMENDATIONS

In view of the statistical findings generated from the analyses conducted by the Applicant and by me, I conclude that tocilizumab 8 mg/kg either as a monotherapy or a combination therapy is efficacious in reducing signs and symptoms of RA after 24 weeks of therapy. There is evidence that tocilizumab 4 mg/kg in combination with MTX therapy is associated with reduction in signs and symptoms of RA after 24 weeks of therapy. There is also enough evidence that tocilizumab demonstrated effects on ACR50 and ACR70 in the various patient populations studied. In addition, changes from baseline for each of the ACR core set parameters are also consistent with the composite scores

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 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

7 APPENDIX

Appendix 1:

The extended Mantel-Haenszel method as described by the Applicant is as follows:

The weighted difference in proportions is the difference in the ACR20 response rates in the TCZ 8 mg/kg treatment group compared with the MTX treatment group, adjusted for site and disease duration. The number of patients in each strata is defined as n_{ijk} where i is the site CRTN, j is the disease duration (≤ 2 years, > 2 years), and k is treatment group (MTX or TCZ 8 mg/kg). The number of events in each strata is denoted by x_{ijk} , where i , j and k are as above. The proportion of ACR20 responders in each strata will be calculated by:

$$p_{ijk} = \frac{x_{ijk}}{n_{ijk}} \quad \text{where } i, j \text{ and } k \text{ are as above.}$$

Difference in Proportions for each Strata

The difference in proportions for each strata will then be calculated as the proportion of patients in each strata in the TCZ 8 mg/kg treatment group minus the proportion of patients in each strata in the MTX treatment group and denoted $d_{ij} = p_{ijTCZ} - p_{ijMTX}$, for i and j as above.

Weights for each Strata

The weights for each strata (i, j) will be calculated as follows:

$$w_{ij} = \frac{n_{ijTCZ} * n_{ijMTX}}{n_{ijTCZ} + n_{ijMTX}}$$

Weighted Differences in Proportions

Within each strata, the weighted differences in the proportions in each of the treatment groups will be calculated as follows:

$$wd_{ij} = w_{ij}d_{ij}$$

and then summed:

$$WD = \sum_i \sum_j wd_{ij}$$

The next stages will be for the calculation of the 95% confidence interval.

Continuity-corrected Proportions

$$p_{ijk}^{\#} = \frac{x_{ijk} + 0.5}{n_{ijk} + 1}$$

Variations

$$Up\ var_{ij} = w_{ij}^2 \left[p_{ijTCZ}^{\#} \frac{(1 - p_{ijTCZ}^{\#})}{n_{ijTCZ}} + p_{ijTCZ}^{\#} \frac{(1 - p_{ijTCZ}^{\#})}{n_{ijMTX}} \right]$$

To calculate the sum of the weights and variations over all strata:

Sum over strata

$$W = \sum_i \sum_j w_{ij}$$

$$Var = \sum_i \sum_j Up\ var_{ij}$$

Point Estimate and Standard Error

$$d = \frac{WD}{W}$$

$$se = \sqrt{\frac{Var}{W^2}}$$

Stratified 95% Confidence Interval

$$\text{Lower Limit} = d - 1.96se$$

$$\text{Upper Limit} = d + 1.96se$$

Appendix 2: Hierarchical Ordering of Secondary Endpoints for Individual Studies

Order	Secondary Endpoint	Comparison (using primary imputation method and population)	Point at which significance can no longer be claimed (studies WA17823, WA18062 and WA17824)
1	Proportion of patients with ACR50 response at 24 weeks.	8 mg/kg + MTX versus Placebo + MTX	
2	Proportion of patients with ACR70 response at 24 weeks.	8 mg/kg + MTX versus Placebo + MTX	
3	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Tender Joint Count	8 mg/kg + MTX versus Placebo + MTX	
4	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Swollen Joint Count	8 mg/kg + MTX versus Placebo + MTX	
5	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Pain VAS	8 mg/kg + MTX versus Placebo + MTX	WA17824

Order	Secondary Endpoint	Comparison (using primary imputation method and population)	Point at which significance can no longer be claimed (studies WA17823, WA18062 and WA17824)
6	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - CRP	8 mg/kg + MTX versus Placebo + MTX	
7	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Physician global VAS	8 mg/kg + MTX versus Placebo + MTX	
8	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Patient Global VAS	8 mg/kg + MTX versus Placebo + MTX	
9	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - ESR	8 mg/kg + MTX versus Placebo + MTX	
10	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - HAQ	8 mg/kg + MTX versus Placebo + MTX	
11	Change in Disease Activity Score (DAS28) from baseline at 24 weeks.	8 mg/kg + MTX versus Placebo + MTX	
12	Proportion of patients with DAS28 score <2.6 at 24 weeks	8 mg/kg + MTX versus Placebo + MTX	
13	Proportion of patients classified as categorical DAS28 responders (EULAR response) at 24 weeks.	8 mg/kg + MTX versus Placebo + MTX	
14	Change in Hemoglobin from baseline at 24 weeks	8 mg/kg + MTX versus Placebo + MTX	
15	ACRn at week 24	8 mg/kg + MTX versus Placebo + MTX	
16	Change in Disease Activity Score (DAS28) from baseline at 24 weeks.	4 mg/kg + MTX versus Placebo + MTX	

Order	Secondary Endpoint	Comparison (using primary imputation method and population)	Point at which significance can no longer be claimed (studies WA17823, WA18062 and WA17824)
17	FACIT fatigue scale scores at 24 weeks.	8 mg/kg + MTX versus Placebo + MTX	WA17823
18	SF-36 at 24 weeks – Physical component score	8 mg/kg + MTX versus Placebo + MTX	
19	SF-36 at 24 weeks – Mental Component score	8 mg/kg + MTX versus Placebo + MTX	WA18062
20	Change in Hemoglobin from baseline at 24 weeks	4 mg/kg +MTX versus Placebo + MTX	
21	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - ESR	4 mg/kg +MTX versus Placebo + MTX	
22	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Physician global VAS	4 mg/kg +MTX versus Placebo + MTX	
23	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - CRP	4 mg/kg +MTX versus Placebo + MTX	
24	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Pain VAS	4 mg/kg +MTX versus Placebo + MTX	
25	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Swollen Joint Count	4mg/kg + MTX versus Placebo + MTX	
26	Proportion of patients with ACR50 response at 24 weeks.	4 mg/kg +MTX versus Placebo + MTX	
27	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Patient Global VAS	4 mg/kg +MTX versus Placebo + MTX	

Order	Secondary Endpoint	Comparison (using primary imputation method and population)	Point at which significance can no longer be claimed (studies WAI7823, WAI8062 and WAI7824)
28	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - Tender Joint Count	4 mg/kg +MTX versus Placebo + MTX	
29	Proportion of patients with ACR70 response at 24 weeks.	4 mg/kg +MTX versus Placebo + MTX	
30	Mean changes from baseline in the individual parameters of ACR core set at 24 weeks - HAQ	4 mg/kg +MTX versus Placebo + MTX	
31	Proportion of patients with DAS28 score <2.6 at 24 weeks	4 mg/kg +MTX versus Placebo + MTX	
32	Proportion of patients classified as categorical DAS28 responders (EULAR response) at 24 weeks.	4 mg/kg +MTX versus Placebo + MTX	
33	ACRn at week 24	4 mg/kg +MTX versus Placebo + MTX	
34	FACIT fatigue scale scores at 24 weeks.	4 mg/kg +MTX versus Placebo + MTX	
35	SF-36 at 24 weeks - Physical component score	4 mg/kg +MTX versus Placebo + MTX	
36	SF-36 at 24 weeks -Mental Component score	4 mg/kg +MTX versus Placebo + MTX	

* Note that there was no break in the hierarchical testing of secondary endpoints for studies WAI7822 and WAI8063.

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Appendix 3: Summary of Baseline Demographic, Baseline Rheumatoid Arthritis Characteristics and Baseline ACR Demographics (ITT Population) – Study WA17822

	PLACEBO + MIX N = 204	MRA 4MG/KG + MIX N = 213	MRA 8MG/KG + MIX N = 205
Sex			
FEMALE	159 (78%)	175 (82%)	175 (85%)
MALE	45 (22%)	38 (18%)	30 (15%)
n	204	213	205
Age in years			
Mean	50.6	51.4	50.8
SD	12.06	12.82	11.76
SEM	0.84	0.88	0.82
Median	51.5	51.0	52.0
Min-Max	22 - 81	20 - 78	20 - 77
n	204	213	205
Height in cm			
Mean	163.1	161.6	161.6
SD	9.81	9.35	8.48
SEM	0.69	0.64	0.60
Median	163.0	160.0	162.0
Min-Max	140 - 199	136 - 191	133 - 181
n	203	213	203
Weight in kg			
Mean	71.6	69.9	68.0
SD	16.98	17.45	15.58
SEM	1.19	1.20	1.09
Median	69.5	67.3	66.0
Min-Max	41 - 125	37 - 146	40 - 123
n	202	212	204
Race Category			
WHITE	149 (73%)	159 (75%)	148 (72%)
ASIAN	25 (12%)	22 (10%)	25 (12%)
AMERICAN INDIAN OR ALASKA NATIVE	19 (9%)	22 (10%)	19 (9%)
BLACK	1 (<1%)	1 (<1%)	2 (<1%)
OTHER	10 (5%)	9 (4%)	11 (5%)
n	204	213	205
Ethnicity			
HISPANIC	63 (31%)	68 (32%)	62 (30%)
NON-HISPANIC	138 (68%)	144 (68%)	143 (70%)
NOT KNOWN	1 (<1%)	1 (<1%)	-
n	202	213	205
Reproductive Status			
NA	-	-	1 (<1%)
POSTMENOPAUSAL	72 (45%)	85 (49%)	93 (53%)
SURGICALLY STERIL.	34 (21%)	31 (18%)	27 (15%)
WITH CONT. PROT.	53 (33%)	59 (34%)	55 (31%)
n	159	175	176
Does the Patient Smoke?			
NO	176 (86%)	173 (81%)	177 (86%)
YES	28 (14%)	40 (19%)	28 (14%)
n	204	213	205
Family History of Coronary Heart Disease?			
NO	191 (94%)	196 (92%)	187 (91%)
YES	13 (6%)	17 (8%)	18 (9%)
n	204	213	205

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 For reproductive status, NA stands for Not Applicable
 For reproductive status, Cont. Prot. means Contraceptive Protection
 DM11 20FEB2007:17:51:05 (PDRD)

	ELDEBO + MIX N = 204	ERA 4MG/KG + MIX N = 213	ERA 8MG/KG + MIX N = 205
Duration of RA (years)			
Mean	7.78	7.43	7.47
SD	7.210	7.430	7.252
SEM	0.505	0.509	0.509
Median	5.94	4.62	5.21
Min-Max	0.3 - 38.2	0.5 - 46.5	0.2 - 39.5
n	204	213	205
Number of Previous DMARDs/ Anti-TNFs			
Mean	1.7	1.5	1.5
SD	1.51	1.36	1.36
SEM	0.11	0.09	0.10
Median	1.0	1.0	1.0
Min-Max	0 - 8	0 - 8	0 - 6
n	204	213	205
Baseline Rheumatoid Factor			
NEGATIVE	60 (29%)	46 (22%)	34 (17%)
POSITIVE	144 (71%)	167 (78%)	171 (83%)
n	204	213	205
CRP			
Mean	6.822	6.785	6.820
SD	0.8723	0.9096	0.9214
SEM	0.0611	0.0626	0.0644
Median	6.828	6.892	6.894
Min-Max	3.99 - 8.75	4.33 - 9.18	3.76 - 8.94
n	204	211	205
Oral Steroid Use			
NO	93 (46%)	96 (45%)	93 (45%)
YES	111 (54%)	117 (55%)	112 (55%)
n	204	213	205
Baseline MIX dose mg/week			
Mean	14.8	14.7	14.5
SD	4.22	4.25	4.41
SEM	0.30	0.29	0.31
Median	15.0	15.0	15.0
Min-Max	10 - 25	8 - 25	10 - 25
n	201	213	205

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 DM11 17APR2007:09:31:43 (PDR)

	PLACERBO + MIX N = 204	PPA 2MG/KG + MIX N = 213	PPA 4MG/KG + MIX N = 205
Tender Joint Count			
Mean	32.8	33.2	31.9
SD	16.05	15.62	15.47
SEM	1.12	1.07	1.06
Median	29.0	31.0	30.0
Min-Max	8 - 68	5 - 68	8 - 68
n	204	213	205
Swollen Joint Count			
Mean	20.7	20.0	19.5
SD	11.71	10.91	11.33
SEM	0.82	0.75	0.79
Median	18.0	17.0	16.0
Min-Max	6 - 63	6 - 56	6 - 61
n	204	213	205
ESR mm/hr			
Mean	49.7	49.2	51.2
SD	26.32	26.78	26.61
SEM	1.84	1.83	1.86
Median	42.5	44.0	45.0
Min-Max	2 - 130	1 - 140	2 - 135
n	204	213	205
CRP mg/dL			
Mean	2.363	2.787	2.608
SD	2.7763	3.4413	2.5979
SEM	0.1944	0.2358	0.1814
Median	1.510	1.770	1.870
Min-Max	0.07 - 16.30	0.05 - 18.50	0.02 - 18.60
n	204	213	205
HbQ			
Mean	1.5	1.6	1.6
SD	0.63	0.64	0.62
SEM	0.05	0.05	0.05
Median	1.5	1.8	1.6
Min-Max	0 - 3	0 - 3	0 - 3
n	169	177	170
Pain VAS (100mm)			
Mean	57.3	60.7	59.9
SD	22.15	20.96	22.44
SEM	1.55	1.44	1.57
Median	57.5	62.0	64.0
Min-Max	10 - 100	12 - 100	2 - 100
n	204	211	205
Patient VAS (100mm)			
Mean	63.6	65.6	64.8
SD	21.82	20.86	22.15
SEM	1.53	1.44	1.55
Median	65.0	69.0	68.0
Min-Max	10 - 100	4 - 100	3 - 100
n	204	211	205
Physician VAS (100mm)			
Mean	63.7	63.6	64.0
SD	14.80	15.79	15.30
SEM	1.04	1.08	1.07
Median	65.0	65.0	65.0
Min-Max	27 - 97	23 - 99	13 - 100
n	203	212	205

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 FML1 20REB2007-17:31:07 (PDR)

Source: CSR WA17822, page 98-100

Appendix 4: Summary of Baseline Demographic, Baseline Rheumatoid Arthritis Characteristics and Baseline ACR Demographics (ITT Population) – Study WA17823

	PLAZAEO + MIX N = 393	MIX 4MG/KG + MIX N = 399	MIX 8MG/KG + MIX N = 398
Sex			
MALE	65 (17%)	63 (16%)	73 (18%)
FEMALE	328 (83%)	336 (84%)	325 (82%)
n	393	399	398
Age in years			
Mean	51.3	51.4	53.4
SD	12.41	12.59	11.72
SEM	0.63	0.63	0.59
Median	52.0	51.0	54.0
Min-Max	19 - 82	21 - 84	18 - 84
n	393	399	398
Height in cm			
Mean	162.1	162.3	162.0
SD	8.71	8.20	9.06
SEM	0.44	0.41	0.46
Median	161.0	162.0	161.0
Min-Max	140 - 188	140 - 196	138 - 196
n	391	396	395
Weight in kg			
Mean	73.8	73.2	72.1
SD	20.27	17.96	16.92
SEM	1.03	0.90	0.85
Median	70.0	70.2	69.5
Min-Max	35 - 149	38 - 143	36 - 130
n	391	396	395
Race Category			
AMERICAN INDIAN OR ALASKA NATIVE	15 (4%)	19 (5%)	13 (3%)
ASIAN	22 (6%)	20 (5%)	26 (7%)
BLACK	16 (4%)	23 (6%)	21 (5%)
OTHER	62 (16%)	57 (14%)	58 (15%)
WHITE	278 (71%)	280 (70%)	280 (70%)
n	393	399	398
Ethnicity			
HISPANIC	142 (36%)	137 (34%)	138 (35%)
NON-HISPANIC	251 (64%)	262 (66%)	260 (65%)
n	393	399	398
Reproductive Status			
3/4	-	-	1 (<1%)
N/A	1 (<1%)	-	-
NA	1 (<1%)	2 (<1%)	-
POSTMENOPAUSAL	158 (40%)	154 (46%)	186 (57%)
SURGICALLY STERIL.	65 (21%)	74 (22%)	75 (23%)
WITH CONT. PROT.	100 (30%)	108 (32%)	63 (19%)
n	329	338	325
Does the Patient Smoke?			
NO	333 (85%)	333 (83%)	323 (81%)
YES	60 (15%)	66 (17%)	75 (19%)
n	393	399	398
Family History of Coronary Heart Disease			
NO	340 (87%)	347 (87%)	348 (87%)
YES	53 (13%)	52 (13%)	50 (13%)
n	393	399	398

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 For reproductive status, NA stands for Not Applicable
 For reproductive status, Cont. Prot. means Contraceptive Protection
 For reproductive status, 3 means "surgically sterilized" and 4 "postmenopausal"
 DML1 27JUL2007:01:43:06 (PDR)

	PLACEBO + MIX N = 393	MSA 4MG/KG + MIX N = 399	MSA 8MG/KG + MIX N = 398
Duration of RA (years)			
Mean	8.94	9.43	9.29
SD	8.060	7.869	8.311
SEM	0.407	0.394	0.417
Median	6.41	7.45	7.44
Min-Max	0.5 - 44.3	0.5 - 43.2	0.6 - 49.9
n	393	399	398
Number of Previous IMARDs/ Anti-INEs			
Mean	1.6	1.7	1.6
SD	1.50	1.44	1.42
SEM	0.08	0.07	0.07
Median	1.0	1.0	1.0
Min-Max	0 - 10	0 - 8	0 - 6
n	393	399	398
Baseline Rheumatoid Factor			
NEGATIVE	72 (18%)	77 (19%)	68 (17%)
POSITIVE	321 (82%)	322 (81%)	330 (83%)
n	393	399	398
CRP28			
Mean	6.533	6.508	6.553
SD	0.9590	0.9406	0.9596
SEM	0.0489	0.0473	0.0484
Median	6.524	6.479	6.652
Min-Max	3.68 - 8.96	3.63 - 8.77	3.66 - 8.94
n	385	395	393
Oral Steroid Use			
NO	128 (33%)	134 (34%)	156 (39%)
YES	265 (67%)	265 (66%)	242 (61%)
n	393	399	398
Baseline MIX dose mg/week			
Mean	14.9	14.9	15.4
SD	4.23	4.25	10.60
SEM	0.21	0.21	0.53
Median	15.0	15.0	15.0
Min-Max	8 - 25	10 - 25	10 - 210
n	393	398	398

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 DM11 22AUG2007-13:30:31 (PIRD)

	PLACERB + MIX N = 393	MRA 4MG/KG + MIX N = 399	MRA 8MG/KG + MIX N = 398
Tender Joint Count			
Mean	27.9	27.9	29.3
SD	14.80	14.15	15.22
SEM	0.75	0.71	0.76
Median	25.0	26.0	26.0
Min-Max	8 - 68	8 - 68	8 - 68
n	393	399	398
Swollen Joint Count			
Mean	16.6	17.0	17.3
SD	9.23	9.78	9.48
SEM	0.47	0.49	0.48
Median	15.0	15.0	15.0
Min-Max	6 - 65	6 - 66	6 - 66
n	393	399	398
ESR mm/hr			
Mean	46.5	45.9	46.4
SD	24.69	25.12	24.80
SEM	1.25	1.26	1.25
Median	42.0	40.0	41.0
Min-Max	4 - 126	1 - 125	1 - 140
n	390	397	396
CRP mg/dL			
Mean	2.235	2.076	2.337
SD	2.5068	2.3892	2.6065
SEM	0.1265	0.1196	0.1307
Median	1.390	1.280	1.540
Min-Max	0.02 - 18.60	0.02 - 16.80	0.04 - 19.50
n	393	399	398
HbO			
Mean	1.5	1.5	1.5
SD	0.62	0.64	0.60
SEM	0.03	0.03	0.03
Median	1.6	1.5	1.6
Min-Max	0 - 3	0 - 3	0 - 3
n	368	376	375
Pain VAS (100mm)			
Mean	55.3	53.3	55.7
SD	22.07	21.97	22.34
SEM	1.12	1.10	1.12
Median	55.0	53.0	57.0
Min-Max	0 - 100	0 - 100	0 - 100
n	368	397	395
Patient VAS (100mm)			
Mean	63.1	61.0	62.7
SD	23.36	23.25	22.49
SEM	1.15	1.17	1.13
Median	65.0	63.0	66.0
Min-Max	0 - 100	0 - 100	0 - 100
n	368	397	395
Physician VAS (100mm)			
Mean	63.1	62.3	62.7
SD	17.34	16.80	16.90
SEM	0.88	0.85	0.85
Median	65.0	64.0	64.0
Min-Max	14 - 100	3 - 99	3 - 100
n	391	395	395

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 PM11 27JUL2007:01:09:04 (PDRD)

Source: CSR WA17823, page 94-97

Appendix 5: Summary of Baseline Demographic, Baseline Rheumatoid Arthritis Characteristics and Baseline ACR Demographics (ITT Population) – Study WA17824

	MIX N = 259	ETA RMC/RG N = 265
Sex		
FEMALE	211 (81%)	219 (83%)
MALE	48 (19%)	46 (17%)
n	259	265
Age in years		
Mean	50.1	51.1
SD	12.83	13.05
SEM	0.80	0.80
Median	50.0	52.0
Min-Max	19 - 83	18 - 79
n	259	265
Height in cm		
Mean	163.0	162.3
SD	9.58	9.37
SEM	0.60	0.58
Median	162.0	162.0
Min-Max	138 - 195	130 - 191
n	258	264
Weight in kg		
Mean	72.6	73.4
SD	18.45	17.74
SEM	1.15	1.09
Median	69.5	70.6
Min-Max	40 - 131	41 - 150
n	258	264
Race Category		
WHITE	188 (73%)	187 (71%)
ASIAN	20 (8%)	22 (8%)
AMERICAN INDIAN OR ALASKA NATIVE	21 (8%)	27 (10%)
BLACK	11 (4%)	10 (4%)
OTHER	19 (7%)	19 (7%)
n	259	265
Ethnicity		
HISPANIC	72 (28%)	82 (31%)
NON-HISPANIC	187 (72%)	183 (69%)
n	259	265
Reproductive Status		
NA	2 (<1%)	1 (<1%)
POSTMENOPAUSAL	89 (42%)	101 (46%)
SURGICALLY STERIL.	52 (24%)	44 (20%)
SURGICALLY STERILIZED / POSTMENOPAUSAL	1 (<1%)	4 (2%)
WITH CONTR. PROT.	69 (32%)	70 (32%)
n	213	220
Does the Patient Smoke?		
NO	208 (80%)	212 (80%)
YES	51 (20%)	53 (20%)
n	259	265
Family History of Coronary Heart Disease?		
NO	241 (93%)	245 (92%)
YES	18 (7%)	20 (8%)
n	259	265

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 For reproductive status, NA stands for Not Applicable
 For reproductive status, Contr. Prot. means Contraceptive Protection
 Primary PP = All Patients excluding Placebo Patients
 11/11 10JUL2007:07:16:55 (2 of 2) [EDRD]

	MIX N = 259	MEA 8ML/KC N = 265
Duration of RA (years)		
Mean	6.31	6.43
SD	7.915	7.652
SEM	0.492	0.470
Median	3.16	3.24
Min-Max	0.2 - 49.6	0.1 - 44.7
n	259	265
Number of Previous IMARDs/ Anti-TNFs		
Mean	1.1	1.2
SD	1.38	1.33
SEM	0.09	0.08
Median	1.0	1.0
Min-Max	0 - 7	0 - 7
n	259	265
Baseline Rheumatoid Factor		
NEGATIVE	65 (25%)	67 (25%)
POSITIVE	194 (75%)	198 (75%)
n	259	265
DAS28		
Mean	6.777	6.779
SD	0.8808	1.0010
SEM	0.0548	0.0616
Median	6.766	6.831
Min-Max	3.70 - 8.82	3.64 - 9.14
n	259	264
Oral Steroid Use		
NO	137 (53%)	137 (52%)
YES	122 (47%)	128 (48%)
n	259	265
MIX Naive		
NO	88 (34%)	89 (34%)
YES	171 (66%)	176 (66%)
n	259	265

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 Primary PP = All Patients excluding Placebo Patients

IM11 10JUL2007:07:19:13

(1 of 1)

	FIX N = 259	ESA BIC/KC N = 265
Tender Joint Count		
Mean	31.1	32.2
SD	13.85	14.70
SEM	0.86	0.90
Median	30.0	31.0
Min-Max	9 - 68	8 - 68
n	259	265
Swollen Joint Count		
Mean	18.9	19.3
SD	10.33	11.21
SEM	0.64	0.69
Median	16.0	17.0
Min-Max	6 - 66	6 - 65
n	259	265
ESR mm/hr		
Mean	48.9	49.9
SD	26.23	27.55
SEM	1.63	1.69
Median	42.0	45.0
Min-Max	1 - 140	3 - 142
n	259	265
CRP mg/dL		
Mean	2.985	2.926
SD	3.3668	3.2361
SEM	0.2092	0.1988
Median	1.930	1.770
Min-Max	0.03 - 22.70	0.02 - 18.40
n	259	265
H2O		
Mean	1.5	1.6
SD	0.63	0.65
SEM	0.04	0.04
Median	1.6	1.6
Min-Max	0 - 3	0 - 3
n	258	265
Pain VAS (100mm)		
Mean	61.3	59.2
SD	20.37	22.45
SEM	1.27	1.38
Median	61.0	61.0
Min-Max	0 - 101	0 - 100
n	259	265
Patient VAS (100mm)		
Mean	65.4	64.0
SD	19.46	21.48
SEM	1.21	1.32
Median	67.5	67.0
Min-Max	8 - 102	5 - 100
n	258	264
Physician VAS (100mm)		
Mean	63.2	63.2
SD	16.31	15.72
SEM	1.02	0.97
Median	64.0	64.0
Min-Max	13 - 96	15 - 100
n	258	265

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 Primary EP = All Patients excluding Placebo Patients
 BML1 10JUL2007-07:21:26 (2 of 2) [PDED]

Source: CSR WA17824, page 119 - 124

Appendix 6: Summary of Baseline Demographic, Baseline Rheumatoid Arthritis Characteristics and Baseline ACR Demographics (ITT Population) – Study WA18062

	MLX/ESQ + MIX N = 158	MRA 481/KC + MIX N = 161	MRA 882/KC + MIX N = 170
Sex			
FEMALE	125 (79%)	130 (81%)	143 (84%)
MALE	33 (21%)	31 (19%)	27 (16%)
n	158	161	170
Age in years			
Mean	53.4	50.9	53.9
SD	13.26	12.46	12.66
SEM	1.05	0.98	0.97
Median	55.0	53.0	55.0
Min-Max	20 - 83	19 - 78	21 - 82
n	158	161	170
Height in cm			
Mean	164.8	165.0	164.1
SD	8.19	8.65	8.64
SEM	0.66	0.68	0.67
Median	165.0	164.0	163.0
Min-Max	142 - 187	147 - 191	141 - 168
n	156	161	168
Weight in kg			
Mean	75.4	76.4	74.3
SD	18.88	18.12	18.50
SEM	1.50	1.43	1.42
Median	72.7	74.1	69.5
Min-Max	43 - 145	45 - 143	43 - 140
n	158	161	170
Race Category			
WHITE	150 (95%)	144 (89%)	152 (89%)
ASIAN	1 (<1%)	4 (2%)	5 (3%)
BLACK	3 (2%)	10 (6%)	7 (4%)
OTHER	2 (1%)	-	5 (3%)
AMERICAN INDIAN OR ALASKAN NATIVE	2 (1%)	3 (2%)	1 (<1%)
n	158	161	170
Ethnicity			
HISPANIC	17 (11%)	22 (14%)	23 (14%)
NA	1 (<1%)	-	1 (<1%)
NON-HISPANIC	140 (89%)	139 (86%)	146 (86%)
n	158	161	170
Reproductive Status			
NA	-	1 (<1%)	-
POSTMENOPAUSAL	56 (45%)	48 (37%)	70 (49%)
SURGICALLY STERIL.	37 (30%)	46 (35%)	40 (28%)
WITH CONTR. PROT.	31 (25%)	36 (27%)	33 (23%)
WITHOUT CONTR. PROT.	1 (<1%)	-	-
n	125	131	143
Does the Patient Smoke?			
NO	120 (76%)	117 (73%)	136 (80%)
YES	38 (24%)	44 (27%)	34 (20%)
n	158	161	170
Family History of Coronary Heart Disease?			
NA	-	1 (<1%)	-
NO	121 (77%)	119 (74%)	133 (78%)
YES	37 (23%)	41 (25%)	37 (22%)
n	158	161	170

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 For reproductive status, NA stands for Not Applicable
 For reproductive status, Contr. Prot. means Contraceptive Protection
 EM11 11JUN2007:14:40:37

SEM = Standard error of the mean

	PLA/CSO + MTX N = 158	MRA 4ML/KG + MTX N = 161	MRA 8ML/KG + MTX N = 170
Duration of RA (years)			
Mean	11.36	10.98	12.59
SD	9.215	8.458	9.325
SEM	0.733	0.667	0.715
Median	8.09	9.34	10.63
Min-Max	0.8 - 53.3	0.9 - 46.6	0.8 - 62.0
n	158	161	170
No. of previous Anti-TNFs			
1	67 (42%)	75 (47%)	85 (50%)
2	69 (44%)	66 (41%)	55 (32%)
3 OR MORE	22 (14%)	20 (12%)	30 (18%)
n	158	161	170
No. of previous DMARDs			
Mean	2.1	2.0	1.9
SD	1.59	1.63	1.66
SEM	0.13	0.13	0.13
Median	2.0	2.0	2.0
Min-Max	0 - 7	0 - 6	0 - 7
n	158	161	170
Baseline Rheumatoid Factor			
NEGATIVE	40 (25%)	44 (27%)	36 (21%)
POSITIVE	118 (75%)	117 (73%)	134 (79%)
n	158	161	170
DA528			
Mean	6.801	6.776	6.791
SD	1.0551	0.9741	0.9286
SEM	0.0850	0.0773	0.0712
Median	6.767	6.849	6.739
Min-Max	3.62 - 8.94	4.33 - 8.81	4.56 - 8.67
n	154	159	170
Oral Steroid Use			
NO	67 (42%)	67 (42%)	82 (48%)
YES	91 (58%)	94 (58%)	88 (52%)
n	158	161	170
Baseline MTX dose mg/week			
Mean	16.5	16.2	15.7
SD	4.78	5.01	4.42
SEM	0.38	0.39	0.34
Median	15.0	15.0	15.0
Min-Max	3 - 25	8 - 25	10 - 25
n	158	161	170
Time of discontinuation of anti-TNF* in Days			
Mean	127.9	123.5	125.7
SD	161.13	134.29	119.42
SEM	12.82	10.65	9.16
Median	83.5	75.0	84.0
Min-Max	14 - 1705	14 - 1117	17 - 896
n	158	159	170

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 * prior to baseline

DM11 11JUN2007:14:39:34

(PDR Page 1 of 1)

	PLACEBO + MTX N = 158	MRA 4MS/KG + MTX N = 161	MRA 8MS/KG + MTX N = 170
Tender Joint Count			
Mean	30.4	31.3	31.7
SD	16.75	15.11	15.40
SEM	1.33	1.15	1.18
Median	28.5	30.0	31.0
Min-Max	5 - 68	8 - 68	8 - 67
n	156	161	170
Swollen Joint Count			
Mean	18.9	19.5	18.9
SD	11.14	10.36	10.91
SEM	0.89	0.82	0.84
Median	15.5	18.0	16.0
Min-Max	4 - 50	6 - 52	6 - 56
n	158	161	170
ESR mm/hr			
Mean	54.6	51.3	49.1
SD	32.72	28.31	27.93
SEM	2.61	2.23	2.14
Median	45.0	43.0	40.0
Min-Max	9 - 186	11 - 140	5 - 133
n	157	161	170
CRP mg/dL			
Mean	3.705	3.113	2.796
SD	4.1182	3.6088	3.3795
SEM	0.3276	0.2844	0.2587
Median	2.260	1.690	1.435
Min-Max	0.02 - 24.10	0.02 - 18.10	0.02 - 18.50
n	158	161	170
HAQ			
Mean	1.7	1.7	1.7
SD	0.62	0.55	0.59
SEM	0.05	0.04	0.05
Median	1.8	1.8	1.9
Min-Max	0 - 3	0 - 3	0 - 3
n	157	159	170
Pain VAS (100mm)			
Mean	64.1	63.5	64.7
SD	21.84	22.17	20.56
SEM	1.75	1.76	1.58
Median	65.0	68.0	69.0
Min-Max	0 - 100	0 - 100	10 - 100
n	155	158	170
Patient VAS (100mm)			
Mean	70.9	70.4	70.2
SD	21.07	23.75	19.98
SEM	1.69	1.88	1.53
Median	75.0	76.0	74.0
Min-Max	0 - 100	0 - 100	18 - 100
n	155	159	170
Physician VAS (100mm)			
Mean	67.5	66.5	66.4
SD	16.05	16.09	17.97
SEM	1.28	1.28	1.35
Median	69.0	69.0	70.0
Min-Max	22 - 100	20 - 100	14 - 100
n	157	159	168

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 DM11 11JUN2007:14:40:38 (EPDR Page 1 of 1)

Source: CSR WA18062, page 101 - 104

Appendix 7: Summary of Baseline Demographic, Baseline Rheumatoid Arthritis Characteristics and Baseline ACR Demographics (ITT Population) – Study WA18063

	PLACEBO + IMPAD N = 413	MSE EMS/KS + DMARD N = 803
Sex		
FEMALE	346 (84%)	654 (81%)
MALE	67 (16%)	149 (19%)
n	413	803
Age in years		
Mean	53.5	53.0
SD	13.13	12.57
SEM	0.65	0.44
Median	54.0	54.0
Min-Max	19 - 83	18 - 89
n	413	803
Height in cm		
Mean	163.0	162.9
SD	8.96	9.49
SEM	0.44	0.34
Median	162.0	162.0
Min-Max	141 - 196	130 - 198
n	413	800
Weight in kg		
Mean	73.3	74.0
SD	18.36	18.26
SEM	0.90	0.65
Median	70.0	71.0
Min-Max	36 - 139	36 - 138
n	413	801
Race Category		
WHITE	297 (72%)	580 (72%)
ASIAN	41 (10%)	76 (9%)
AMERICAN INDIAN OR ALASKA NATIVE	35 (8%)	84 (10%)
BLACK	27 (7%)	36 (4%)
OTHER	13 (3%)	27 (3%)
n	413	803
Ethnicity		
HISPANIC	97 (23%)	206 (26%)
NON-HISPANIC	316 (77%)	597 (74%)
n	413	803
Reproductive Status		
3/4	1 (<1%)	1 (<1%)
NA	3 (<1%)	11 (2%)
POSTMENOPAUSAL	155 (44%)	315 (47%)
SURGICALLY STERIL.	101 (29%)	171 (26%)
WITH CONTR. PROT.	89 (26%)	166 (25%)
n	349	664
Does the Patient Smoke?		
NO	343 (83%)	668 (83%)
YES	70 (17%)	135 (17%)
n	413	803
Family History of Coronary Heart Disease?		
NO	351 (85%)	689 (86%)
YES	60 (15%)	114 (14%)
n	411	803

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 For reproductive status, NA stands for Not Applicable
 For reproductive status, Contr. Prot. means Contraceptive Protection
 DM11 15MAY2007-04:20:32 (1 of 1) (PDRD)

	PLAQUEO + DMARD N = 413	MRX SMC/KC + DMARD N = 803
Duration of RA (years)		
Mean	9.79	9.80
SD	9.082	8.784
SEM	0.447	0.310
Median	6.84	7.03
Min-Max	0.5 - 44.4	0.4 - 46.1
n	413	802
Number of Previous DMARDs/ Anti-TNFs		
Mean	1.6	1.6
SD	1.61	1.63
SEM	0.08	0.06
Median	1.0	1.0
Min-Max	0 - 8	0 - 9
n	413	803
Baseline Rheumatoid Factor		
NEGATIVE	102 (25%)	179 (22%)
POSITIVE	311 (75%)	624 (78%)
n	413	803
DRS28		
Mean	6.645	6.685
SD	0.8957	1.0258
SEM	0.0452	0.0363
Median	6.677	6.736
Min-Max	2.95 - 8.93	2.15 - 9.18
n	409	797
Oral Steroid Use		
NO	186 (45%)	393 (49%)
YES	227 (55%)	410 (51%)
n	413	803
Number of Background DMARDs		
1	311 (75%)	616 (77%)
2	82 (20%)	152 (19%)
3 OR MORE	15 (4%)	26 (3%)
NO BACKGROUND DMARD	5 (1%)	9 (1%)
n	413	803
Baseline Azathioprine dose (mg/day)		
Mean	83.3	102.8
SD	43.30	36.27
SEM	14.43	8.55
Median	50.0	100.0
Min-Max	50 - 150	50 - 150
n	5	18
Baseline Chloroquine dose (mg/week)		
Mean	1317.6	1464.6
SD	350.87	553.32
SEM	75.22	79.87
Median	1050.0	1400.0
Min-Max	450 - 1750	500 - 3500
n	27	48
Baseline Hydroxychloroquine dose (mg/week)		
Mean	2329.1	2338.4
SD	738.54	703.94
SEM	99.58	65.36
Median	2800.0	2800.0
Min-Max	700 - 4200	700 - 4200
n	55	116

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 DM11 20JUL2007:17:32:05 (cont.) (PDR)

	PLACEDO + IMARD N = 413	MRA 8MG/KG + IMARD N = 803
Baseline Leflunomide dose (mg/day)		
Mean	18.44	18.94
SD	3.651	3.438
SEM	0.458	0.351
Median	20.00	20.00
Min-Max	8.6 - 20.0	8.6 - 30.0
n	65	96
Baseline Background IMARD MTX dose (mg/week)		
Mean	14.99	14.73
SD	5.019	5.077
SEM	0.288	0.206
Median	15.00	15.00
Min-Max	2.5 - 25.0	2.5 - 25.0
n	304	609
Baseline Parenteral Gold dose (mg/week)		
Mean	40.00	30.75
SD	10.000	27.224
SEM	5.774	19.250
Median	40.00	30.75
Min-Max	30.0 - 50.0	11.5 - 50.0
n	3	2
Baseline Sulfasalazine dose (mg/day)		
Mean	1948.3	1984.4
SD	671.73	744.80
SEM	88.20	72.34
Median	2000.0	2000.0
Min-Max	1000 - 4000	500 - 4000
n	58	106

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 DM11 20JUL2007:17:32:05 (1 of 1) (PDR)

	PLACEBO + DMARD	MRZ 3MG/KG + DMARD
	N = 413	N = 803
Tender Joint Count		
Mean	29.1	30.1
SD	14.76	15.96
SEM	0.73	0.56
Median	27.0	26.0
Min-Max	2 - 68	6 - 68
n	412	803
Swollen Joint Count		
Mean	18.7	19.7
SD	10.79	11.62
SEM	0.53	0.41
Median	16.0	17.0
Min-Max	1 - 63	2 - 66
n	412	803
ESR mm/hr		
Mean	49.2	48.2
SD	28.30	27.47
SEM	1.39	0.97
Median	42.0	41.0
Min-Max	1 - 150	1 - 163
n	413	803
CRP mg/dL		
Mean	2.634	2.551
SD	4.6582	3.1539
SEM	0.2292	0.1113
Median	1.370	1.530
Min-Max	0.02 - 77.20	0.02 - 37.20
n	413	803
H2O		
Mean	1.5	1.5
SD	0.62	0.62
SEM	0.03	0.02
Median	1.6	1.5
Min-Max	0 - 3	0 - 3
n	411	794
Pain VAS (100mm)		
Mean	58.5	58.4
SD	23.39	22.52
SEM	1.16	0.80
Median	61.0	60.0
Min-Max	0 - 100	0 - 100
n	410	798
Patient VAS (100mm)		
Mean	65.5	66.2
SD	23.71	22.68
SEM	1.17	0.80
Median	70.0	69.0
Min-Max	2 - 100	0 - 100
n	410	797
Physician VAS (100mm)		
Mean	63.4	63.6
SD	16.89	16.46
SEM	0.83	0.58
Median	64.5	65.0
Min-Max	10 - 100	10 - 98
n	412	801

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
 DM11 13MAY2007:04:21:00 (1 of 1) (PDED)

Source: CSR WA18063, page 97-100

Appendix 8: ACR_n at Week 24 derivation rule

The derivation rule requires that percent TJC and percent SJC and at least 3 out of 5 components are non-missing.

Take the third highest non-missing value (from an ascending order i.e. biggest improvement to lowest improvement) of the following 5 tests (raw percent VAS pain, raw percent VAS patient global, raw percent VAS physician global, raw percent HAQ score, raw percent CRP score). Note that if the raw percent CRP score is missing then use raw percent ESR.

Then take the Maximum of (third highest non-missing value above, percent SJC (LOCF) and percent TJC (LOCF)) and finally multiplying it by -1. The result is multiplied by -1 to show improvement as a positive value.

Also where a patient has taken a steroid within 8 weeks prior to week 24 then set ACR response to 'Nonresponder' (i.e. ACR_n=).

If percent SJC (LOCF) is missing or percent TJC (LOCF) is missing or at least three of the remaining components are missing or third highest non-missing value of the 5 tests is missing then set ACR response to 'Nonresponder' (i.e. ACR_n=).

Appendix 9: Proportion of ACR20 responders by Week, in %

Study WA17822

	Sponsor's			Reviewer's		
	Placebo + MTX N=204	TCZ4mg/kg +MTX N=213	TCZ 8 mg/kg + MTX N=205	Placebo + MTX N=204	TCZ4mg/kg +MTX N=213	TCZ 8 mg/kg + MTX N=205
Week 2	7%	20%	25%	7%	21%	27%
Week 4	10%	29%	38%	11%	31%	39%
Week 8	25%	43%	49%	26%	51%	44%
Week 12	28%	53%	62%	26%	53%	61%
Week 16	31%	56%	63%	31%	56%	62%
Week 20	24%	52%	66%	24%	51%	66%
Week 24	27%	48%	59%	27%	48%	59%

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

Study WA17823

	Sponsor's			Reviewer's		
	Placebo + MTX N=393	TCZ4mg/kg +MTX N=399	TCZ 8 mg/kg + MTX N=398	Placebo + MTX N=393	TCZ4mg/kg +MTX N=399	TCZ 8 mg/kg + MTX N=398
Week 2	9%	18%	22%	9%	17%	23%
Week 4	15%	28%	34%	16%	31%	34%
Week 8	22%	42%	48%	23%	42%	47%
Week 12	26%	51%	51%	26%	51%	52%
Week 16	30%	48%	53%	30%	48%	52%
Week 20	28%	48%	56%	28%	48%	57%
Week 24	27%	51%	56%	27%	51%	56%

* Reviewer: just re-analysis using the same criteria, i.e. LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'

Study WA18062

	Sponsor's			Reviewer's		
	Placebo + MTX N=158	TCZ 4 mg/kg + MTX N=161	TCZ 8 mg/kg + MTX N=170	Placebo + MTX N=158	TCZ 4 mg/kg + MTX N=161	TCZ 8 mg/kg + MTX N=170
Week 2	10%	12%	17%	9%	14%	17%
Week 4	11%	16%	26%	11%	18%	26%
Week 8	16%	27%	43%	15%	29%	43%
Week 12	15%	39%	44%	17%	38%	44%
Week 16	13%	32%	45%	11%	32%	44%
Week 20	13%	29%	54%	13%	29%	55%
Week 24	10%	30%	50%	11%	31%	51%

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

Study WA18063

	Sponsor's		Reviewer's	
	Placebo + DMARD N=413	TCZ 8 mg/kg + DMARD N=803	Placebo + DMARD N=413	TCZ 8mg/kg +DMARD N=803
Week 2	7%	20%	8%	21%
Week 4	15%	34%	16%	34%
Week 8	22%	50%	22%	50%
Week 12	23%	55%	22%	56%
Week 16	23%	62%	22%	62%
Week 20	25%	62%	25%	63%
Week 24	25%	61%	24%	61%

* Reviewer: just re-analysis using the same criteria, i.e. LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'

Study WA17824

	Sponsor's		Reviewer's	
	MTX only N=284	TCZ8mg/kg only N=286	MTX only N=284	TCZ8mg/kg only N=286
Week 2	10%	24%	10%	26%
Week 4	22%	37%	23%	40%
Week 8	34%	56%	36%	58%
Week 12	46%	60%	47%	60%
Week 16	48%	64%	47%	64%
Week 20	58%	70%	56%	68%
Week 24	52%	70%	52%	70%

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

Appendix 10: ACR Core Components - Study WA17822

Table 23 Change from Baseline in the ACR Core Set Parameters at Week 24 - ANOVA Results (ITT Population)

etanvarcfbacrwk24i Analysis of Variance of Change from Baseline in ACR Core Set Parameters at Week 24 (ITT Population)

	Swollen Joint Count (66 joint count)	Tender Joint Count (66 joint count)	Patient's Global VAS (mm)	Physician's Global VAS (mm)	Patient's Pain VAS (mm)	CRP (mg/dL)	ESR (mm/hr)	HQO-DI
Placebo + MIX								
n	204	204	173	173	123	122	122	101
Adjusted mean	-4.3	-7.4	-17.8	-32.7	-14.0	-0.353	-7.1	-0.34
NSA 4mg/kg + MIX								
n	211	211	156	158	156	157	157	126
Adjusted mean	-8.5	-14.5	-28.8	-38.3	-25.0	-1.656	-25.5	-0.52
Difference*	-4.2	-7.0	-10.9	-5.6	-11.0	-1.303	-18.3	-0.18
95% CI for Difference	(-6.1, -2.3)	(-10.0, -4.1)	(-17.1, -4.8)	(-10.5, -0.8)	(-17.0, -5.0)	(-2.018, -0.593)	(-24.3, -12.4)	(-0.34, -0.02)
p-value	<.0001	<.0001	0.0005	0.0229	0.0004	0.0004	<.0001	0.0296
NSA 8mg/kg + MIX								
n	205	205	173	173	173	172	174	141
Adjusted mean	-10.5	-17.1	-32.7	-41.6	-29.8	-2.509	-39.5	-0.55
Difference*	-6.2	-9.6	-14.9	-9.0	-15.8	-2.156	-32.3	-0.21
95% CI for Difference	(-8.1, -4.2)	(-12.6, -6.7)	(-20.9, -8.9)	(-13.8, -4.2)	(-21.7, -9.9)	(-2.857, -1.455)	(-38.2, -26.5)	(-0.37, -0.05)
p-value	<.0001	<.0001	<.0001	0.0002	<.0001	<.0001	<.0001	0.0082

* Adjusted mean difference
All comparisons to Placebo+ MIX
LOCF used for tender and swollen joint counts, no imputation used for missing HQO score, CRP, ESR and VAS assessments.
All assessments are set to missing from the time a patient receives escape therapy and only pre-escape therapy joint count assessments are carried forward.

Program : \$PROD/cdpl1935/etanvarcfbacr.sas / Output : \$PROD/cdpl1935/wa17822/reports/etanvarcfbacrwk24i.r17

22FEE2007 16:29
Source Clinical Study Report, page 121

Appendix 11: ACR Core Components - Study WAI7823

Table 22 Change from Baseline in the ACR Core Set Parameters at Week 24 - ANOVA Results (ITT Population)

etanvarcfbacr#24i Analysis of Variance of Change from Baseline in ACR Core Set Parameters at Week 24 (ITT Population)

	Swollen		Tender		Patient's Global VAS (mm)	Physician's Global VAS (mm)	Patient's Pain VAS (mm)	CRP (mg/dL)	ESR (mm/hr)	HQ-DI
Placebo + MIX										
n	391	391	391	391	213	214	213	214	211	197
Adjusted mean	-2.5	-4.9	-18.4	-28.2	-13.1	-28.2	-13.1	-0.1367	-7.1	-0.30
MRA 4mg/kg + MIX										
n	399	399	308	307	308	307	308	308	304	292
Adjusted mean	-7.4	-12.1	-24.9	-34.0	-19.3	-34.0	-19.3	-0.7031	-19.4	-0.41
Difference*	-4.8	-7.2	-6.5	-5.8	-6.2	-6.2	-6.2	-0.5664	-12.3	-0.10
95% CI for Difference	(-6.1, -3.5)	(-9.2, -5.2)	(-11.4, -5.2)	(-9.6, -1.9)	(-10.9, -1.5)	(-9.6, -1.9)	(-10.9, -1.5)	(-1.0020, -0.1307)	(-16.7, -8.0)	(-0.20, -0.00)
P-value	<.0001	<.0001	0.0088	0.0037	0.0098	0.0037	0.0098	0.0109	<.0001	0.0456
MRA 8mg/kg + MIX										
n	397	397	316	320	317	320	317	321	318	301
Adjusted mean	-8.5	-14.0	-25.7	-36.3	-22.2	-36.3	-22.2	-1.8947	-34.6	-0.50
Difference*	-5.9	-9.1	-7.3	-10.1	-3.1	-10.1	-3.1	-1.7580	-27.5	-0.19
95% CI for Difference	(-7.2, -4.6)	(-11.1, -7.1)	(-12.1, -2.4)	(-14.0, -6.2)	(-13.9, -4.4)	(-14.0, -6.2)	(-13.9, -4.4)	(-2.1929, -1.3230)	(-31.9, -23.2)	(-0.30, -0.09)
P-value	<.0001	<.0001	0.0036	<.0001	0.0002	<.0001	0.0002	<.0001	<.0001	0.0002

* Adjusted mean difference
 All comparisons to Placebo+ MIX
 LOCF used for tender and swollen joint counts, no imputation used for missing HQ score, CRP, ESR and VAS assessments
 All assessments are set to missing from the time a patient receives escape therapy and only pre-escape therapy joint count assessments are carried forward.

Program : #HQB/cdpl1985/etanvarcfbacr.sas / Output : #HQB/cdpl1985u/WI7823a/reports/etanvarcfbacr#24i.rtf
 21JUN2007 1:53

Source: Clinical Study Report, page 113

Appendix 12: ACR Core Components - Study WA18062

Table 33 Change from Baseline in the ACR Core Set Parameters at Week 24 - ANOVA Results (ITT Population)

etanarctfbcwr#24i Analysis of Variance of Change from Baseline in ACR Core Set Parameters at Week 24 (ITT Population)

	Swollen Joint Count (66 joint count)	Tender Joint Count (66 joint count)	Patient's Global VAS (mm)	Physician's Global VAS (mm)	Patient's Pain VAS (mm)	CRP (mg/dL)	ESR (mm/hr)	HAQ-DI
Placebo + MIX								
n	157	157	61	61	61	63	62	62
Adjusted mean	-0.5	0.3	-15.4	-20.0	-8.6	-0.0600	-3.0	-0.05
MRA 5mg/kg + MIX								
n	160	160	106	106	106	106	107	106
Adjusted mean	-6.8	-10.5	-25.4	-30.5	-21.0	-1.4034	-19.7	-0.31
Difference*	-6.2	-10.8	-10.0	-10.5	-12.4	-1.3434	-16.7	-0.25
95% CI for Difference	(-9.0, -3.5)	(-14.6, -7.1)	(-20.3, 0.3)	(-18.6, -2.5)	(-22.1, -2.6)	(-2.5411, -0.1456)	(-25.4, -8.1)	(-0.42, -0.09)
P-value	<.0001	<.0001	0.0577	0.0107	0.0131	0.0281	0.0002	0.0029
MRA 8mg/kg + MIX								
n	170	170	129	127	129	129	129	130
Adjusted mean	-7.8	-14.8	-32.8	-38.2	-32.5	-2.5807	-37.2	-0.39
Difference*	-7.2	-15.1	-17.4	-18.2	-23.9	-2.5207	-34.2	-0.34
95% CI for Difference	(-9.3, -4.5)	(-18.8, -11.4)	(-27.8, -7.0)	(-26.3, -10.0)	(-33.7, -14.1)	(-3.7210, -1.3203)	(-43.0, -25.5)	(-0.51, -0.17)
P-value	<.0001	<.0001	0.0011	<.0001	<.0001	<.0001	<.0001	<.0001

* Adjusted mean difference
 All comparisons to Placebo+ MIX
 IDDF used for tender and swollen joint counts, no imputation used for missing HAQ score, CRP, ESR and VAS assessments.
 All assessments are set to missing from the time a patient receives escape therapy and only pre-escape therapy joint count assessments are carried forward.

Program : \$PROD/cdpl1935/wa18062/etanarctfbcwr.sas / Output : \$PROD/cdpl1935/wa18062/reports/etanarctfbcwr#24i.r17
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Source: Clinical Study Report, page 129

Appendix 13: ACR Core Components – Study WA18063

Table 25 Change from Baseline in the ACR Core Set Parameters at Week 24: ANOVA Results (ITT Population)

etanvarcfbacrnk24i Analysis of Variance of Change from Baseline in ACR Core Set Parameters at Week 24 (ITT Population)

	Swollen Joint Count (66 joint count)	Tender Joint Count (68 joint count)	Patient's Global VAS (mm)	Physician's Global VAS (mm)	Patient's Pain VAS (mm)	CRP (mg/dL)	ESR (mm/hr)	HQ-DI
Placebo + DCRD	411	411	322	322	322	324	325	322
n								
Adjusted mean	-4.9	-8.5	-16.3	-21.6	-12.8	-0.2652	-4.7	-0.20
1522 Emg/kg + DCRD	801	801	729	733	730	727	732	724
n								
Adjusted mean	-10.3	-15.7	-33.2	-35.9	-29.9	-2.1947	-35.6	-0.47
Difference*	-5.5	-7.1	-16.9	-14.4	-17.1	-1.9295	-30.9	-0.27
95% CI for Difference	(-6.7, -4.3)	(-8.9, -5.4)	(-20.5, -13.4)	(-17.3, -11.4)	(-20.3, -13.4)	(-2.3190, -1.5400)	(-34.2, -27.6)	(-0.34, -0.20)
P-value	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

* Adjusted mean difference
 LACF used for tender and swollen joint counts, no imputation used for missing HQ score, CRP, ESR and VAS assessments
 All assessments are set to missing from the time a patient receives escape therapy and only pre-escape therapy joint count assessments are carried forward.

Program : \$PROD/cobp11935/etanvarcfbacr.sas / Output : \$PROD/cobp11935/wa18063/reports/etanvarcfbacrnk24i.r17
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Source: Study Report, page 126

Appendix 14: ACR Core Components – Study WA17824

Table 33 Change from Baseline in the ACR Core Set Parameters at Week 24 – ANOVA Results – Primary Analysis Group (ITT Population)

etanvarcfbacrw424ip Analysis of Variance of Change from Baseline in ACR Core Set Parameters at Week 24 – All Patients excluding Placebo Patients (ITT Population)

	Swollen Joint Count (66 joint count)	Tender Joint Count (68 joint count)	Patient's Global VAS (mm)	Physician's Global VAS (mm)	Patient's Pain VAS (mm)	CRP (mg/dL)	ESR (mm/hr)	HAQ-DI
EMX								
n	281	281	249	249	251	250	249	250
Adjusted mean	-8.2	-13.9	-30.7	-31.7	-29.9	-1.8669	-16.1	-0.52
MPA 8mg/kg								
n	285	285	258	259	259	259	257	258
Adjusted mean	-11.7	-17.2	-34.5	-31.3	-31.9	-2.7588	-37.3	-0.70
Difference*	-3.5	-3.3	-3.8	-9.6	-2.0	-0.8919	-21.1	-0.18
95% CI for Difference	(-5.2, -1.7)	(-5.9, -0.6)	(-6.9, 1.3)	(-13.5, -5.6)	(-6.9, 3.0)	(-1.5015, -0.2824)	(-26.0, -16.2)	(-0.30, -

* Adjusted mean differences
LOCF used for tender and swollen joint counts, no imputation used for missing HAQ score, CRP, ESR and VAS assessments.
All assessments are set to missing from the time a patient receives escape therapy and only pre-escape therapy joint count assessments are carried forward.
Program : \$PROC/ua17824/etanvarcfbacr.sas / Output : \$PROD/cepl1985/j17824a/reports/etanvarcfbacrw424ip.r17
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Appendix 15: Patient Disposition – Extension Studies WA18695-WA18696

Study		Placebo	TCZ4mg/kg	TCZ8mg/kg	MTX	Total
WA17822*	Randomized	204	213	205		622
	Complete 24 wks	189 (93%)	186 (87%)	191 (93%)		566 (91%)
	#Treated Extension					537 (95%)
	ACR20 at Wk 24					213 (40%)
	Withdrew					67 (12%)
	Adverse Events					32
	Lack of Efficacy					11
Died					1	
Others					23	
Escape					104 (19%)	
WA17824†	Randomized	99		286	284	669
	Complete 24 wks	82 (83%)		268 (94%)	262 (92%)	612 (91%)
	#Treated Extension					473 (77%)
	ACR20 at Wk 24					251 ()
	Withdrew					29 ()
	Adverse Events					9
	Lack of Efficacy					5
Died					1	
Others					14	
Escape					26 ()	
WA18062*	Randomized	158	161	170		489
	Complete 24 wks	126 (80%)	136 (84%)	147 (87%)		409 (84%)
	#Treated Extension					398 (81%)
	ACR20 at Wk 24					200 ()
	Withdrew					59 ()
	Adverse Events					19
	Lack of Efficacy					23
Died					5	
Others					12	
Escape					106 ()	
WA18063**	Randomized	413		803		1216
	Complete 24 wks	371 (90%)		752 (94%)		1123 (92%)
	#Treated Extension					1031 (92%)
	ACR20 at Wk 24					496 ()
	Withdrew					100 ()
	Adverse Events					44
	Lack of Efficacy					19
Died					3	
Others					34	
Escape					56 ()	

* +MTX

** +DMARDs

† Monotherapy

Appendix 16: Summary of the Primary Endpoint by each Subgroup – Study WA17822

		Placebo + MTX	TCZ 4 mg/kg+MTX	TCZ 8 mg/kg + MTX
Study WA17822	Overall	N=204 54 (27%)	N=213 102 (48%) *	N=205 120 (59%) *
Sex	Male	n=45 11 (24%)	n=38 20 (53%)	n=30 16 (53%)
	Female	n=159 43 (27%)	n=175 82 (47%)	n=175 104 (59%)
Race	White	n=149 41 (28%)	n=159 66 (42%)	n=148 84 (57%)
	Others*	n=55 13 (24%)	n=54 36 (67%)	n=57 36 (63%)
Age	< 50	n=90 25 (28%)	n=93 42 (45%)	n=84 53 (63%)
	50 – 64	n=89 23 (26%)	n=85 40 (47%)	n=98 55 (56%)
	65 – 75	n=20 5 (25%)	n=32 18 (56%)	n=21 12 (57%)
	>75	n=5 1 (20%)	n=3 2 (67%)	n=2 0

* Others include Asian (12%), American Indian/ Alaska Native (10%), Black (1%), Hispanic (5%), Arabic (1 subject)

Appendix 17: Summary of the Primary Endpoint by each Subgroup – Study WA17823

		Placebo + MTX	TCZ 4 mg/kg+MTX	TCZ 8 mg/kg + MTX
Study WA17823	Overall	N=392 106 (27%)	N=399 202 (51%) *	N=399 224 (56%) *
Sex	Male	n=65 17 (26%)	n=63 34 (54%)	n=73 36 (49%)
	Female	n=328 89 (27%)	n=336 168 (50%)	n=325 188 (58%)
Race	White	n=278 74 (27%)	n=280 145 (52%)	n=280 156 (56%)
	Others*	n=115 32 (28%)	n=119 57 (48%)	n=118 68 (58%)
Age	< 50	n=157 44 (28%)	n=177 97 (55%)	n=126 84 (67%)
	50 – 64	n=180 52 (29%)	n=156 75 (48%)	n=208 104 (50%)
	65 – 75	n=53 8 (15%)	n=60 27 (45%)	n=56 32 (57%)
	>75	n=3 2 (67%)	n=6 3 (50%)	n=8 4 (50%)

* Others include Asian (6%), American Indian/ Alaska Native (4%), Black (5%), Others (14%)

Appendix 18: Summary of the Primary Endpoint by each Subgroup – Study WA18062

		Placebo + MTX	TCZ 4 mg/kg+MTX	TCZ 8 mg/kg + MTX
Study WA18062	Overall	N=158 16 (10%)	N=161 49 (30%) *	N=170 85 (50%) *
Sex	Male	n=33 5 (15%)	n=31 13 (42%)	n=27 16 (59%)
	Female	n=125 11 (9%)	n=130 36 (28%)	n=143 69 (48%)
Race	White	n=150 14 (9%)	n=144 44 (31%)	n=152 78 (51%)
	Others*	n=8 2 (25%)	n=17 5 (29%)	n=18 7 (39%)
Age	< 50	n=61 8 (13%)	n=66 21 (32%)	n=56 33 (59%)
	50 – 64	n=61 5 (8%)	n=74 19 (26%)	n=82 42 (51%)
	65 – 75	n=30 3 (10%)	n=20 8 (40%)	n=22 6 (28%)
	>75	n=6 0	n=1 1 (100%)	n=10 4 (40%)

* Others include Asian (2%), American Indian/ Alaska Native (1%), Black (4%), Other(1%)

Appendix 19: Summary of the Primary Endpoint by each Subgroup- Study WA18063

		Placebo + DMARD	TCZ 8 mg/kg + DMARD
Study WA18063	Overall	N=413 101 (24%)	N=803 488 (61%) *
Sex	Male	n=67 18 (27%)	n=149 94 (63%)
	Female	n=346 83 (24%)	n=654 394 (60%)
Race	White	n=297 66 (22%)	n=580 351 (61%)
	Others*	n=116 35 (30%)	n=223 137 (61%)
Age	< 50	n=143 41 (29%)	n=274 177 (65%)
	50 – 64	n=188 47 (25%)	n=379 226 (60%)
	65 – 75	n=67 12 (18%)	n=135 80 (59%)
	>75	n=15 1 (7%)	n=15 5 (33%)

* Others include Asian (10%), American Indian/ Alaska Native (10%), Black (5%), Other(3%)

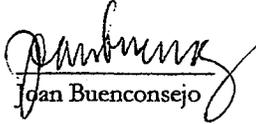
Appendix 20: Summary of the Primary Endpoint by each Subgroup- Study WA17824

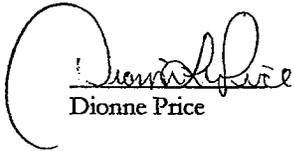
		Placebo + DMARD	TCZ 8 mg/kg + DMARD
Study WA18063	Overall	N=413 101 (24%)	N=803 488 (61%)*
Sex	Male	n=67 18 (27%)	n=149 94 (63%)
	Female	n=346 83 (24%)	n=654 394 (60%)
Race	White	n=297 66 (22%)	n=580 351 (61%)
	Others*	n=116 35 (30%)	n=223 137 (61%)
Age	< 50	n=143 41 (29%)	n=274 177 (65%)
	50 – 64	n=188 47 (25%)	n=379 226 (60%)
	65 – 75	n=67 12 (18%)	n=135 80 (59%)
	>75	n=15 1 (7%)	n=15 5 (33%)

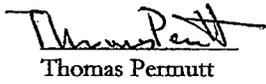
* Others include Asian (10%), American Indian/ Alaska Native (10%), Black (5%), Other(3%)

8 SIGNATURE PAGE

Biometrics Division


Joan Buenconsejo 07/23/08
Date


Dionne Price 7/23/08
Date


Thomas Permutt 7/25/08
Date