U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	STN 125276/S022 (Cross references: IND 11972)
Drug Name:	Actemra® (Tocilizumab)
Indication(s):	Treatment of Active Systemic Juvenile Idiopathic Arthritis In Patients 2 Years of Age and Older
Applicant:	Hoffman-La Roche, Inc.
Date(s):	Received date: 10/14/10; PDUFA date: 04/01/11
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Keywords: Clinical Studies, BLA review

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Roche, proposes Actemra® injection for treatment of active Systemic Juvenile idiopathic Arthritis in patients 2 years of age and older. Based on evaluation of JIA ACR30 response with absence of fever after 12 weeks treatment, the applicant claims Actemra® is effective in improving JIA ACR30 response with absence of fever, reducing systemic features, and enabling corticosteroid dose reduction in sJIA patients; these effectiveness were maintained in the open labeling extension through 44 weeks of treatment. My review of the statistical evidence suggests support for the claim of improving JIA ACR30 response with absence of fever. Other efficacy endpoints support this main efficacy finding.

1.2 Brief Overview of Clinical Studies

Actemra® (tocilizumab) was approved on January 8, 2010 for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies (BLA 125276). The purpose of this supplemental Biologic License Application (sBLA) is to provide data in support of the use of Actemra® at the doses of 12 mg/kg for patients weighted <30kg and 8mg/kg for patients weighed ≥30kg given once every 2 weeks for the indication of treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients 2 years of age and older.

In this submission, the review on efficacy was mainly based on study WA18221. This study was an ongoing, three parts, 5 years phase 3 study. Part I consists of a12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of tocilizumab compared to placebo in 112 patients with active sJIA. Part II is a 92-week single arm open-label long-term extension (LTE) to examine the long term use of tocilizumab, followed by Part III, a 3 year open label continuation of the study to examine the long term use of tocilizumab.

1.3 Statistical Issues and Findings

There was no statistical issue identified during the review. The major efficacy findings are the following:

• The treatment effect of tocilizumab administrated through Intravenous Infusion every two weeks was measured by the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR30) with absence of fever (no temperature recording ≥ 37.5˚C in the preceding 7 days) after 12 weeks treatment. Eighty five percent (64/75) of the patients treated with tocilizumab and 24% (9/37) of placebo patients achieved this endpoint. Compared to placebo, the improvement by tocilizumab was 62% with a 95% CI of (45%, 78%), which was

statistically significant and the improvement exceeded the minimum clinical important difference (MCID) of 30%.

• Tocilizumab treated patients had a higher proportion of patients achieving JIA ACR30/50/70/90 responses at week 12 in comparison with the placebo patients. The improvement of tocilizumab in proportions of each JIA ACR response level was statistically significantly compared to placebo. This observed response rate were improved further following continued long-term treatment with tocilizumab.

• Positive effects were shown on joint inflammation, systemic effects, laboratory endpoints, and physical function in tocilizumab treated patients compared to patients treated with placebo;

• The mean concomitant oral corticosteroid dose during tocilizumab treatment decreased over time (>1 year). Over 94% of patients reduced their oral corticosteroid dose by LTE data cut (May 10th 2010).

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Actemra® (tocilizumab, 4mg/kg with an increase to 8 mg/kg based upon clinical response) was approved on January 8, 2010 in the United States for treatment of adult patients (18 years old and above) with moderate to severe active rheumatoid arthritis who have had inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. The purpose of this supplemental Biologic License Application (sBLA) is to provide data in support of the use of Actemra® at the doses of 12 mg/kg for patients weighted <30kg and 8mg/kg for patients weighed ≥30kg given once every 2 weeks for the indication of treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients 2 years of age and older.

sJIA is a subset of juvenile idiopathic arthritis (JIA) that is characterized by the presence of arthritis, intermittent fever, and rash and comprises between 4% and 17% of all cases of JIA. The arthritis can involve any number of joints. According to the applicant, "NSAIDs alone are effective for many children with sJIA. However, if NSAIDs are ineffective second-line agents such as methotrexate or corticosteroids may be considered. Methotrexate (MTX) is dosed orally or subcutaneously for sJIA. MTX use in sJIA is limited by its efficacy and side effects such as elevated liver function tests, anemia, and teratogenicity."

Tocilizumab is a recombinant humanized anti-human monoclonal antibody of the IgG1 sub-class directed against the IL-6 receptor and is currently being studied or has been studied in diseases including Castleman's disease, multiple myeloma, SLE, Crohn's disease, adult rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (sJIA). Currently, tocilizumab (8mg/kg administered IV every 2 weeks) was approved for sJIA in children 2 years of age and older in Japan and India.

2.1.2 History of Drug Development

The sJIA clinical development plan was introduced to the Division of Anesthesia, Analgesia, and Rheumatology Products by Roche via IND 11972. The development program consists of one Phase 3 study (WA18221), four supportive studies from Japan (MRA011JP, MRA316JP, MRA317JP, and MRA324JP), and one single-dose EU study (LRO320). Among the four supportive studies, only MRA316JP was a phase 3, double-blind, placebo-control study which provided supportive efficacy evidence. Other three studies were open-label, phase 2 or 3 or a long-term efficacy and safety studies. Protocol WA18221 and its amendment (Protocol Version B, dated June 2009) were reviewed by the Division, and agreements (SPA) were reached on December 5, 2007 and July 30, 2009. Of note, all patients had been recruited into the study and completed at least the week 6 assessment before the implementation and approval of Protocol Version B. The changes were not statistical related.

The SPA was reviewed by the statistical team and the statistical analysis plan, including the analysis of the primary endpoint, randomization approach, and sample size calculation was acceptable. The statistical team did raise two concerns with the clinical team about oral corticosteroid (OCS) tapering and growth endpoints. The statistical reviewer noted that no formal analysis plans were provided to support the statement of 'ability to taper corticosteroids' as well as to evaluate the treatment effect on growth velocity. Although the clinical team is somewhat confident that descriptive information concerning corticosteroid use will be beneficial to clinicians, they are unclear whether the comparative growth curve data will be of sufficient quality and quantity to determine the treatment effect on growth velocity. There is no mention of any exploratory growth analyses in the protocol submitted for SPA.

2.1.3 Specific Studies Reviewed

In this submission, the review of efficacy was mainly based on study WA18221-Part I and data for 50 patients who reached one year in Part II. The Japan's study MRA316JP, included the placebo-control and double-blinded period, had a different patient population, study design, and primary endpoint. This study only served as a supportive study along with others studies from Japan (MRA011JP, MRA317JP, and MRA324JP), and the single-dose EU study (LRO320). Throughout the review, tocilizumab will be referred to as TCZ, methotrexate as MTX, and disease modifying anti-rheumatic drugs as DMARDs, non-steroidal anti-inflammatory drug as NSAID, and corticosteroid as CS.

2.2 Data Sources

All data was supplied by the applicant to the CBER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location `\\...\eCTD Submissions\STN125276\125276.enx`. The information needed for this review was contained in modules 1, 2.7, and 5.3.5.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy Study WA18221

3.1.1 Study Design

Table 1 presents the study design of these two studies which mainly collected efficacy and safety data to support tocilizumab (TCZ) in treatment of active JIA in patients 2 years of age and older.

Table 1: Design of key controlled efficacy studies

Study/Center /Study Period	***Study Design***	***Key Inclusion Criteria***	***# Patients by Group Entered/ Completed***	***Primary Endpoints***
WA18221 – Part I Phase 3 43 sites world-wide Part I: 5/9/2008 to 9/2/2009	Randomized Double-blind Place o0controlled Parallel group Multi-center Consisting of three parts: Part I: 12-week DB period Part II: 92-weeks single-arm open-label extension Part III: 3-year single-arm, open-label continuation of the study	Patients aged 2 to 17 years old with active sJIA who have had an inadequate clinical response to NSAIDs and corticosteroids due to toxicity or lack of efficacy	TCZ 8mg/kg: 37/36 (1 escaped) TCZ 12mg/kg: 38/37 Placebo: 37/36 (20 escaped)	Primary: Responder rate of ACR30 and absence of fever at week 12
MRA316JP Phase 3 8 sites in Japan Japan 5/20/04 to 6/30/05	Multi-center, double-blind, randomized, placebo-controlled, withdrawal study 6 wks followed by 12 wk DB withdrawal phase	Patients aged to Ages 2-19 yrs with active sJIA who had an inadequate clinical response to NSAIDs and corticosteroids due to toxicity or lack of efficacy	TCZ: 8mg/kg q2wksx3 (open phase) followed by 8 mg/kg or placebo q2wksx6 (double-blind withdrawal phase) 56 dosed, 50 completed, 6 withdrawn	Open-label period: Co-Primary: 1. Responder rate of ACR30 at the last observation day 2. Responder rate of improvement in CRP (CRP<0.5mg/dL) on the last observation day Blind period: Primary: Rate of maintained response*

*maintained if the last observations 2 weeks after the sixth infusion in the blind period were completed without the patient being withdrawn from the study based on the withdrawal criteria or without the patient completing the study as a subject of rescue** during the blind period.

** Definition of "subject of rescue": A patient was concluded as being a subject of rescue if either of the following were confirmed during the blind period. Patients who were subjects of rescue completed the study after the last observations had been conducted.

- If CRP increased to ≥1.5 mg/dL
- If the criteria for 30% improvement in the JIA core set (compared with before the first infusion in the open-label period) were not met)

Study WA18221 was an ongoing, three parts, 5 years phase 3 study. Part I consists of a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of tocilizumab compared to placebo in 112 patients with active sJIA. Part II is a 92-week single arm open-label long-term extension (LTE) to examine the long term use of tocilizumab, followed by Part III, a 3 year open label continuation of the study to examine the long term use of tocilizumab.

Part I consists of a 12-week randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of TCZ compared to placebo in patients with active sJIA.

The overall design of the study is depicted in Figure 1.

Following screening, eligible patients were unequally randomized (TCZ: placebo = 2:1) with stratification by body weight (< 30kgs or ≥ 30kgs), disease duration (< 4 years or ≥ 4 years), background CS dose (< 0.3 mg/kg or ≥ 0.3 mg/kg), and background MTX use (Yes or No) to receive either TCZ or placebo intravenously (IV) every two week for 12 weeks. In the TCZ group, patients <30kgs received a dose of 12 mg/kg and patients ≥30kgs received a dose of 8 mg/kg. In Part I of the study, the dose assigned at baseline could not be adjusted for any changes (gain or loss) in body weight (BW) (<30kgs to/from ≥30kgs).

Patients could have their CSs tapered following the CS Guidelines at Week 6 and/or Week 8 if they acquired a JIA American College of Rheumatology (ACR) 70 response, had a normal ESR, and absence of fever* prior to taper. CS reduction was not permitted at Week 10.

* ***Absence of fever*** *defined as no temperature measurement ≥ 37.5° C in the preceding seven days;* ***Presence of fever*** *defined as any measurement ≥ 37.5°C in the preceding seven days.*

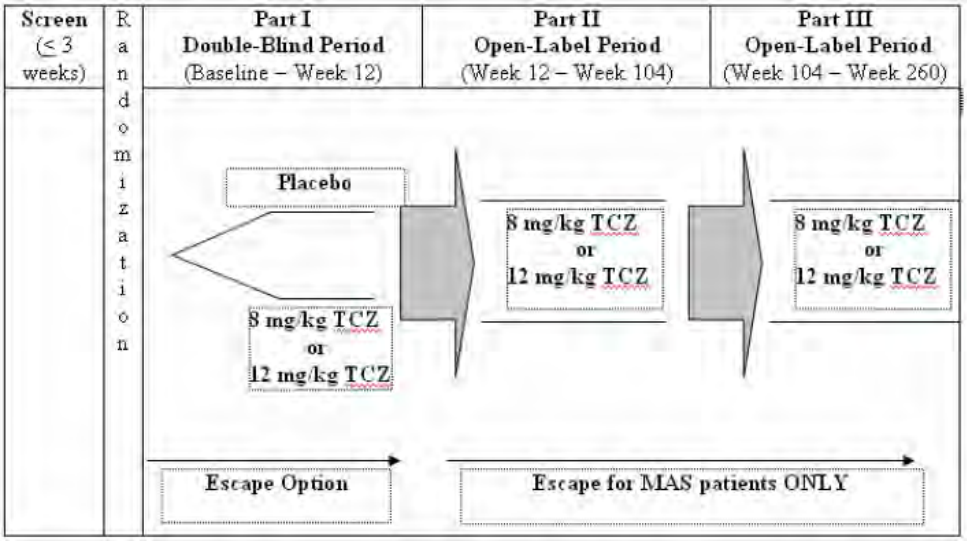
Patients who completed the first six scheduled visits in Part I of the study had the option to enter into the Part II active treatment part of the study where all patients would receive open-label TCZ. Patients who entered escape during Part I (patient can escape at anytime after randomization) and who were benefiting from receiving TCZ were also able to enter Part II. Throughout the study, patients were assessed a minimum of every two weeks for clinical efficacy and safety. Patients who received prohibited therapy were withdrawn from study medication. The end of the study will occur when the last participating patient completes the last scheduled visit of Part III.

Qualified patients can receive early escape therapy at any time after randomization. The collaborative group coordinating centers was used to qualify patients for early escape therapy by applying the following rule:

1. If, in the opinion of the coordinating center, a patient qualifies for escape therapy:
    - At a scheduled visit: treatment with open label active study (when a patients qualified for early escape therapy) drug will be administered at that visit.
    - At an unscheduled visit: treatment with open label active study drug will be administered at the next scheduled visit (see protocol for the detail of criteria for “escape” study medication).
2. Occasionally, there may be a patient who cannot meet the above JIA ACR30 flare criteria due to a high disease burden at study entry.

Patients who enter escape and do not achieve significant clinical improvement after three doses of tocilizumab should be considered for discontinuation of tocilizumab. The reason for escape therapy must be recorded as an adverse event in the eCRF with the start date being the first date escape therapy is given, whether it be with steroids or open label active study drug.

Figure 1: Study Design



3.1.2 Efficacy Endpoints and Assessment Schedule

The primary endpoint is the proportion of patients with at least 30% improvement in JIA core set (JIA ACR30 response) at week 12 (JIA Core Set assessed in comparison to baseline) and absence of fever. Absence of fever defined as no temperature measurement ≥ 37.5°C in the preceding seven days; Presence of fever defined as any measurement ≥ 37.5°C in the preceding seven days.

The following are secondary endpoints that were evaluated:

1 The proportion of patients with fever due to sJIA at baseline who are free of fever at week 12.
2 The proportion of patients with JIA ACR30 response at week 12.
3 The proportion of patients with JIA ACR50 response at week 12.
4 The proportion of patients with an elevated CRP at baseline who have normal CRP at week 12.
5 The percentage CFB in ESR at week 12.
6 The percentage CFB in CHAQ-DI score at week 12.
7 The proportion of patients with JIA ACR70 response at week 12.
8 The percentage CFB in physician's global assessment of disease activity VAS at week 12.
9 The percentage CFB in parent/patient's global assessment of overall well-being VAS at week 12.
10 The proportion of patients with anemia at baseline who increase hgb by ≥10 g/L at week 12.
11 The proportion of patients with anemia at baseline who increase hgb by ≥ 10 g/L at week 6
12 The proportion of patients with rash characteristic of sJIA at baseline who are free of rash at week 12.
13 The CFB in the pain VAS at week 12.
14 The proportion of patients with a minimally important improvement in the CHAQ-DI by week 12.
15 The proportion of patients with JIA ACR30 response at week 12 adjusted for oral CS dose modifications.
16 The proportion of patients receiving oral CSs with a JIA ACR70 response at week 6 or week 8 who then reduce their oral CS dose by at least 20% without subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12.
17 The proportion of patients with JIA ACR90 response at week 12.
18 The proportion of patients with thrombocytosis at baseline who have a normal platelet count at week 12.
19 The proportion of patients with leucocytosis at baseline who have a normal total WBC count at week 12.
20 The proportion of patients with anemia at baseline who have normal hgb at week 12.
21 The percentage CFB in number of joints with active arthritis at week 12.
22 The percentage CFB in number of joints with limitation of movement at week 12.

The schedules of study efficacy assessments for part I periods are presented was every two weeks. Patients who terminate study participation by withdrawing consent will not be required to return for any follow-up assessments. Patients and/or parents/legal guardians who discontinue study medication infusions and are not terminating study participation should return for all withdrawal visits.

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

Of the 126 patients who were screened for the study, 112 patients were randomized and enrolled. Patients were recruited across 43 centers in 17 countries worldwide including:

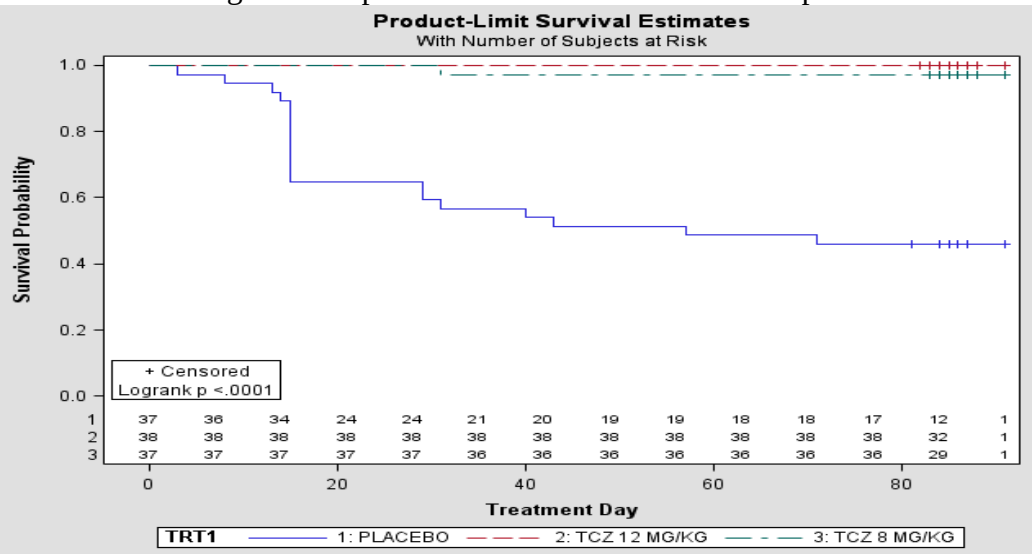
- North America: Canada (2 centers) and United States (10 centers);
- Central America: Mexico (2 centers);
- South America: Argentina (3 centers) and Brazil (2 centers);
- Europe: Belgium (2 centers), Czech Republic (1 center), Germany (3 centers), United Kingdom (2 centers), Greece (3 centers), Italy (4 centers), Netherlands (1 center),Norway (1 center), Poland (1 center), Slovakia (1 center), and Spain (2 centers);
- Rest of world: Australia (3 centers).

A total of 112 patients were enrolled; 109 (97%) completed the 12 weeks of study (Table 2). A total of 21 patients received escape therapy with 20 placebo patients (9 treated with open-label TCZ 8mg/kg and 11 treated with open-label TCZ 12mg/kg) and one TCZ 8mg/kg patient as early as week 1 (Figure 2). All but three patients (patient IDs: 1005, 1664, and 1094) completed 12 weeks of Part I of the study.

Table 2: Patients' Accountability N (%)

Study WA18221-Part I	***Placebo***	***TCZ 8 mg/kg***	***TCZ 12 mg/kg***
Randomized	37	37	38
Completed treatment period without escape therapy	17 (46)	36 (97)	37 (97)
Received escape therapy at any time	20 (54) (9 to TCZ8, 11 to TCZ12)	1 (<1) (to TCZ12)	0
Discontinued	1 (<1)	1 (<1)	1 (<1)
Reason of early discontinuation ST			
Adverse event	1 (<1)	0	1 (<1)
Patient refused treatment	0	1	0
ITT population	37 (100)	37 (100)	38 (100)
PP population	31 (84)	32 (86)	33 (87)

Figure 2: Kaplan-Meier Curve of Time to Escape



In general, baseline demographic, baseline sJIA characteristics, and baseline ACR score were balanced among the treatment groups (Table 3). As a result of the doses assigned based on body weight (i.e. < or ≥ BW 30 kgs), the mean age, BW, height, and body surface area (BSA) were higher in the TCZ 8 mg/kg group in comparison to the TCZ 12 mg/kg group. However, these characteristics were similar between the all TCZ group and the placebo group.

Table 3: Patients' Demographic and Baseline Characteristics N (%)

Study WA18221-Part I	***Placebo (N=37)***	***TCZ 8 mg/kg (N=37)***	***TCZ 12 mg/kg (N=38)***
Age (yrs)			
2-5 years old, N (%)	11 (30)	0	16 (42)
6-12 years old, N (%)	15 (41)	13 (35)	20 (53)
13-18 years old, N (%)	11 (30)	24 (65)	2 (5)
Mean (SD)	9.1 (4.4)	13.5 (2.9)	6.6 (3.3)
Range	2 – 17	7 – 17	2 - 16
Sex			
Female	17 (46)	21 (57)	18 (47)
Male	20 (54)	16 (43)	20 (53)
Race			
Caucasian	32 (87)	35 (95)	32 (84)
Black	0	1 (3)	0
American Indian or Alaska Native	2 (5)	0	0
Other	3 (8)	1 (3)	6 (16)
Weight (kg)			
<30	21 (57)	0	38 (100)
≥30	16 (43)	37 (100)	0
Mean (SD)	31.8 (16.7)	49.7 (20.0)	20.1 (6.0)
Range	10 – 73	30 – 110	10 - 31
Height (cm)			
Mean (SD)	121.2 (20.5)	144.9 (16.2)	107 (14.3)
Range	79 – 160	114 – 174	75 – 133
Body Surface Area (m^2)			
Mean (SD)	1.0 (0.3)	1.4 (0.3)	0.8 (0.2)
Range	0.5 – 1.8	1.0 – 2.2	0.5 – 1.0
Ethnicity, N (%)			
Hispanic	12 (32)	7 (19)	13 (34)
Non-Hispanic	25 (68)	30 (81)	25 (66)
Region, N (%)			
Europe	18 (49)	25 (68)	18 (47)
North America	8 (22)	9 (24)	7 (18)
South America	10 (27)	1 (3)	11 (29)
Rest of World	1 (3)	2 (5)	2 (5)

* Body surface area: BSA (m2) = 0.007184 x [weight (kg)]$^{0.425}$ x [height (cm)]$^{0.725}$

The disease characteristics between the placebo and the TCZ group were similar except for a higher proportion of patients with rash (in the 14 days prior to baseline) in the placebo group (49%) compared with the all TCZ group (29%). In addition, mean baseline CRP was lower in the placebo group (95.6 mg/L) in comparison with the all TCZ group (200.4 mg/L) (Table 4). The sponsor stated that this was due to three patients (two in the TCZ 8 mg/kg (ID=1651 and ID=1373) and one in the TCZ 12 mg/kg group (ID=1372)) had very high CRP values that distorted the mean/median summary statistics. They added that although this was not ideal, the JIA ACR core set includes ESR and not CRP as the APR and this was found to be better matched between the treatment groups.

Fever, an important systemic symptom in sJIA, was present (in the 7 days prior to baseline) in approximately 50% of patients. As a result of the dosing regimen (i.e. dosing based on body weight, < or ≥ BW 30 kgs), the mean number of previous DMARDs and biologics, and Tanner Stage were higher in the TCZ 8 mg/kg group in comparison to the TCZ 12 mg/kg group. However, these characteristics were similar between all TCZ group and the placebo group (Table 4).

Table 4: sJIA Disease Characteristics at Baseline

Study WA18221-Part I	***Placebo (N=37)***	***TCZ 8 mg/kg (N=37)***	***TCZ 12 mg/kg (N=38)***
Fever Status (Last 7 Days prior to baseline)			
Absent	17 (46)	25 (68)	18 (47)
Present	20 (54)	12 (32)	20 (53)
Fever Status (Last 14 Days prior to baseline)			
Absent	13 (35)	22 (59)	12 (32)
Present	24 (65)	15 (41)	26 (68)
Rash Status (Last 14 Days prior to baseline)			
Absent	19 (51)	28 (76)	25 (66)
Present	18 (49)	9 (24) *	13 (34)
No. of Previous DMARDs			
Mean (SD)	1.4 (1.4)	1.6 (1.2)	1.0 (0.9)
Range	0 – 5	0 – 4	0 – 3
No. of Previous DMARDs Category			
0	12 (32)	8 (22)	12 (32)
1	11 (30)	11 (30)	18 (47)
2	9 (24)	8 (22)	5 (13)
≥ 3	5 (14)	10 (27)	3 (8)
No. of Previous Biologics			
Mean (SD)	1.6 (1.3)	2.5 (1.5)	1.4 (1.1)
Range	0 – 5	0 – 6	0 – 4
No. of Previous Biologics Category			
0	8 (22)	2 (5)	10 (26)
1	12 (32)	10 (27)	9 (24)
2	8 (22)	7 (19)	14 (37)
≥3	9 (24)	18 (49)	5 (13)
CRP (mg/L)			
Mean (SD)	95.6 (68.7)	232.2 (534.9)	169.3 (269.0)
Median	77.2	95.2	123.2
Range	2 – 302	9 – 2524	5 - 1704
JADI-A (Articular Damage) (0-72)			
Mean (SD)	5.0 (5.6)	5.3 (7.6)	5.0 (8.3)
Median	3.0	3.5	2.0
Range	0 – 21	0 – 37	0 - 45
JADI-E (Extraarticular Damage) (0-17)			
Mean (SD)	1.7 (1.7)	1.4 (1.8)	1.4 (2.0)
Median	1.0	1.0	1.0
Range	0 – 5	0 – 8	0 – 10
Tanner Stage (1-5)			
Mean (SD)	1.5 (1.0)	3.0 (1.5)	1.1 (0.2)
Median	1.0	3.0	1.0
Range	1 – 5	1 – 5	1 - 2

Fever status: Present = temperature >=37.5 C in past 7/14 days or in past 7 days. Free = no temperature >=37.5 C in past 14 days. * One patient rash assumed due to missing diary data

All six of the JIA ACR core components at baseline were similar between the placebo and all TCZ groups although the mean values were slightly higher in the TCZ patients indicating a potentially higher disease burden (Table 5).

The randomization was effective with a similar proportion of patients in each stratification variable category in the placebo and all TCZ groups (Table 6). Across all patients there was an even split (50/50) in each strata except use of background MTX, which was higher (70% of the patients) compared to those who did not use background MTX.

Table 5: JIA ACR Core Components at Baseline

Study WA18221-Part I	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)
No. of Active Joints (0-71)			
Mean (SD)	16.9 (12.9)	23.5 (16.6)	19.2 (15.2)
Median	13.0	19.0	13.5
Range	5 – 67	5 – 65	3 – 71
No. of Joints with Limitation of Movement (0 – 67)			
Mean (SD)	17.9 (15.9)	23.4 (16.9)	18.1 (14.6)
Median	14.0	20.0	14.5
Range	1 – 67	0 – 65	0 – 67
Patient/Parent Global Assessment VAS (0 – 100 mm)			
Mean (SD)	56.3 (21.2)	61.3 (22.8)	59.3 (25.0)
Median	52.0	61.0	65.5
Range	20 – 100	0 – 100	8 – 100
Physician Global Assessment (VAS) (0 – 100 mm)			
Mean (SD)	61.4 (21.2)	68.1 (15.1)	71.1 (16.2)
Median	63.0	69.0	71.0
Range	13 – 100	17 – 92	28 – 100
CHAQ-DI Score (0 – 3)			
Mean (SD)	1.7 (0.8)	1.7 (0.8)	1.8 (0.8)
Median	1.6	1.9	1.9
Range	0 – 3.0	0 – 3.0	0 – 3.0
ESR (mm/hr)			
Mean (SD)	54.1 (35.4)	50.9 (31.7)	64.1 (29.8)
Median	45	50	69
Range	5 – 140	5 – 130	8 - 130

Table 6: Randomization Stratification Variables at Baseline

Study WA18221-Part I	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)
Weight (kg)			
<30kg	21 (57)	-	38 (100)
≥30kg	16 (43)	37 (100)	-
Duration of sJIA Disease (years)			
Mean (SD)	5.1 (4.4)	6.3 (4.4)	4.0 (3.2)
Median	4.0	5.1	2.8
Range	0.6 – 16.1	0.8 – 15.2	0.5 – 13.3
Duration of sJIA Disease Category			
<4 years	19 (51)	16 (43)	22 (58)
≥4 years	18 (49)	21 (57)	16 (42)
Background Oral CS Dose (mg/kg/day)*			
Mean (SD)	0.27 (0.17)	0.21 (0.15)	0.36 (0.17)
Median	0.28	0.19	0.40
Range	0.0 – 0.5	0.0 - .6	0.0 – 0.9
Background Oral CS Dose Category			
<0.3 mg/kg/day	19 (51)	28 (76)	10 (26)
≥ 0.3 mg/kg/day	18 (49)	9 (24)	28 (74)
Background MTX Use			
No	11 (30)	16 (43)	7 (18)
Yes	26 (70)	21 (57)	31 (82)

* Prednisone equivalent is used in calculation of oral corticosteroid dose.

3.1.4 Statistical Methodologies

The primary (the proportion of patients achieved JIA ACR30 response with absence of fever at week 12) and all categorical secondary efficacy endpoints included in this review were analyzed using a Cochran-Mantel-Haenszel test adjusted for stratification factors used at randomization. The analyses were based on the ITT population defined as all patients who were randomized and who received at least one administration of study medication. Patients who have withdrawn from the study, patients who have received escape therapy, and patients in whom the week 12 primary endpoint results cannot be determined, for whatever reason, was classified as non-responders in the primary analysis.

Other continuous secondary efficacy endpoints included in this review were analysis using analysis of variance (ANOVA) with adjustment for the stratification factors used in randomization. The analyses were based on patients who did not receive the escape therapy. The reviewer's analyses based on the ITT population are also included in this review. The baseline was defined as the latest non-missing assessment prior to the first infusion of double-blind medication. In the absence of data at the baseline visit, data collected at screening was substituted as the baseline value which was acceptable since there was less than 14 days between screening time and baseline visit.

In order to control the rate of false positive conclusions, a fixed sequence approach was applied. The hierarchical ordering of the secondary endpoints is listed above and all comparisons are for TCZ (all patients) versus placebo

The data imputation method specified by the sponsor was the last observation carried forward (LOCF) method.

Categorical endpoints:

Step 1: Patients who entered escape therapy, or withdrawn from the study, or were lost to follow-up prior to or at the time-point at which the endpoint was analyzed was classified as non-responders.
Step 2: In cases where the responder endpoint was determined using the values of one or more continuous parameters, and where one or more of those continuous parameters was missing or partially missing (e.g. a joint from the total count) at a particular time-point visit window, then the missing value(s) of the continuous parameter(s) was imputed using the LOCF principle. The latest available post-baseline value(s) of the continuous endpoint(s) was carried forward and used in the determination of the responder endpoint.
Step 3: In cases where the responder endpoint was determined using the values of one or more categorical parameters, and where one or more of those categorical parameters was missing at a particular time-point visit window, then the patient was classified as a non-responder for the time-point at which the endpoint was assessed.
Step 4: If after application of the above rules the responder endpoint cannot be determined the patient was classified as a non-responder for the endpoint at that time-point.

Continuous Endpoints:

For the standalone endpoints involving a continuous parameter the following missing data handling rules was used, unless otherwise specified:
Step 1: Patients who entered escape therapy, or withdrawn from the study, or was lost to follow-up prior to or at the time-point at which the parameter was analyzed was excluded from analysis.
Step 2: If the parameter was missing at the time-point visit window then the missing value was imputed using the LOCF principle.
Step 3: If after application of the above rules the parameter cannot be determined then the patient was excluded from analysis at that time-point.

Temperature Data

"Absence" of fever was defined as no patient e-diary temperature measurements ≥37.5oC in the 7 days preceding the time-point assessment day (i.e. baseline, week 12 etc.) on which the JIA ACR core components were assessed. The following missing data handling rules was used:
Step 1: If there are <4 days with a temperature recording in the 7 days preceding the time-point assessment day, then the patient will be regarded as having had fever.
Step 2: If there are ≥4 days with a temperature recording in the 7 days preceding the time-point assessment day, then the days for which temperature data was non-missing was used in determining the patient's absence of fever status.

"Free" of fever was defined as no patient e-diary temperature measurements ≥37.5oC in the 14 days preceding the time-point assessment day (i.e. baseline, week 12 etc.) on which the JIA ACR core components were assessed. The following missing data handling rules was used:
Step 1: If there are <8 days with a temperature recording in the 14 days preceding the time-point assessment day, then the patient was regarded as having had fever.
Step 2: If there are ≥8 days with a temperature recording in the 14 days preceding the time-point assessment day, then the days for which temperature data was non-missing was used in determining the patient's free of fever status.

Rash Data

Free of rash was defined as no rash characteristic of sJIA recorded in the patient e-diary in the 14 days preceding the time-point assessment day (i.e. baseline, week 12 etc.) on which the JIA ACR core components were assessed. The following missing data handling rules was used:
Step 1: If there were <8 days with a rash recording in the 14 days preceding the time-point assessment day, then the patient was regarded as having had sJIA rash.
Step 2: If there were ≥8 days with a rash recording in the 14 days preceding the time-point assessment day, then the days for which temperature data was non-missing was used in determining the patient's free of sJIA rash status.

Protocol WA18221 and its amendment (Protocol Version B, dated June 2009) were reviewed and agreements (SPA) were reached on December 5, 2007 and July 30, 2009.

3.1.5 Dose Selection

No dose-ranging study was conducted. The dose regimen of TCZ 8mg/kg every 2 weeks for patients ≥ 30kgs, and TCZ 12mg/kg every 2 weeks for patients < 30kgs were used in this study. The rationale for the dose regimen was based on subgroup analysis and PK modeling in Study MRA316JP. Reader is referred to Dr. Partha Roy's review (the clinical pharmacology reviewer) and Dr. Kathleen Coyle's review (the clinical reviewer) for information regarding the dose selection.

3.1.6 Efficacy Results and Conclusions

The primary efficacy endpoint and all 22 secondary endpoints met the significance level of $p \leq 0.05$. This review presents results of the primary endpoint and secondary endpoints that the applicant is seeking to be included in the Clinical Section of the Label, as well as endpoints that our clinical colleagues deemed relevant.

Proportion of patients with a JIA ACR30 response and absence of fever and other JIA ACR Response Rate at week 12

Sixty-four TCZ patients and nine placebo patients met the primary endpoint criteria of response (i.e. JIA ACR30 responder and absence of fever) at week 12. Of the TCZ patients, 85% responded in contrast to 24% of the placebo patients demonstrating a statistically significant difference (Table 7). Twenty-eight patients (76%) treated with TCZ 8 mg/kg and 36 patients (95%) treated with TCZ 12 mg/kg met the primary endpoint criteria of response, which are also significantly different compared to placebo. The analysis of primary efficacy endpoint was repeated using the PP population and completers and the results were consistent with the results of primary analysis using the ITT population. Of the 85% TCZ treated patients who responded at week 12, two-thirds (57%) started to respond at week 2 (Figure 3). It also appears that majority who responded at week 12 would have responded by week 6.

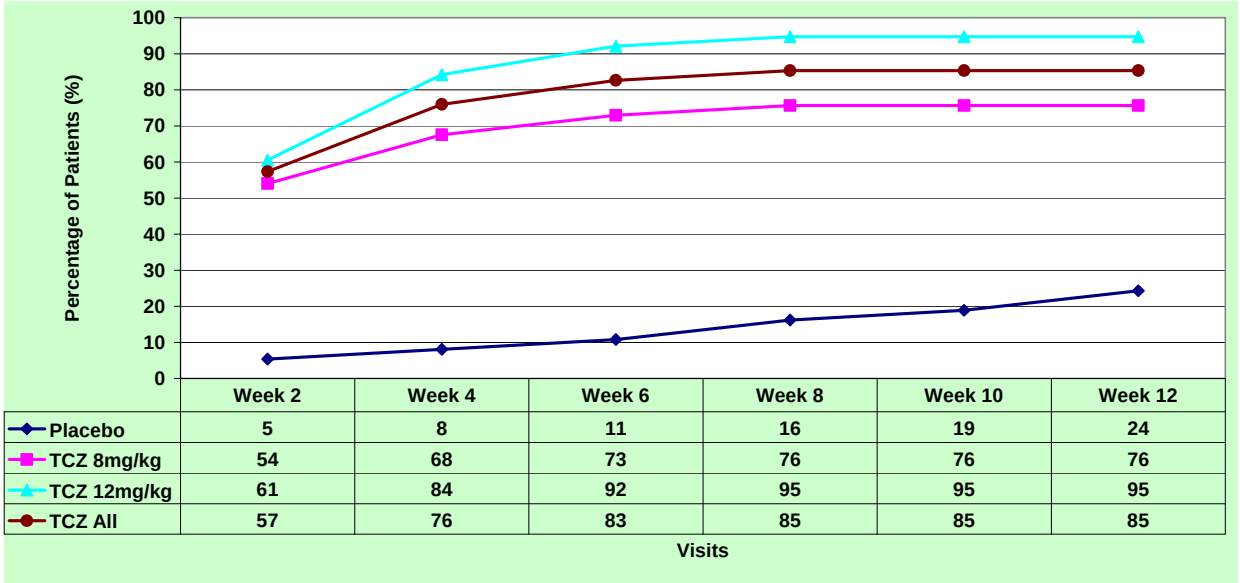
A significantly higher proportion of patients in the TCZ group achieved JIA ACR30/50/70/90 responses at week 12 compared to the placebo group (Table 8 and Figure 4). The proportion of responders was higher for ACR30/50/70/90 in the TCZ 12 mg/kg patients compared to the TCZ 8 mg/kg patients and both groups were significantly different from the placebo group. As shown in Figure 5, a higher proportion of patients in the TCZ groups achieved JIA ACR30/50/70/90 responses over the 12-week period compared to the placebo group.

Table 7: The Results of Primary Efficacy Endpoint Analysis

	Placebo (N=37)	***TCZ 8 mg/kg (N=37)***	***TCZ 12 mg/kg (N=38)***	***All TCZ (N=75)***
ITT Population (Primary analysis population)				
N	37	37	38	75
Responder, N (%)	9 (24)	28 (76)	36 (95)	64 (85)
95% C.I.	(11, 38)	(62, 90)	(88, 100)	(77, 93)
Weighted difference vs. Placebo		52	69	62
95% C.I.		(26, 78)	(47, 90)	(45, 78)
p-value		<0.0001	<0.0001	<0.0001
PP Population (Sensitivity analysis population)				
N	31	32	32	64
Responder, N (%)	9 (29)	25 (78)	31 (97)	56 (79)
95% C.I.	(13, 45)	(64, 92)	(91, 100)	(79, 96)
Weighted difference vs. Placebo		50	63	57
95% C.I.		(19, 80)	(40, 87)	(39, 76)
p-value		0.002	<0.0001	<0.0001
Completers Population (Sensitivity analysis population)				
N	17	36	37	73
Responder, N (%)	9 (53)	28 (78)	36 (97)	64 (88)
95% C.I.	(29, 77)	(64, 91)	(92, 100)	(80, 95)
Weighted difference vs. Placebo		25	47	38
95% C.I.		(-16, 65)	(16, 77)	(14, 62)
p-value		0.2312	0.0025	0.0023

Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at baseline.
Source: primary_analysis.sas;

Figure 3: Start Time of JIA ACR30 with Absence of Fever Responders



	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Placebo	5	8	11	16	19	24
TCZ 8mg/kg	54	68	73	76	76	76
TCZ 12mg/kg	61	84	92	95	95	95
TCZ All	57	76	83	85	85	85

Table 8: The JIA ACR Response Rates at Week 12

	Placebo (N=37)	***TCZ 8 mg/kg (N=37)***	***TCZ 12 mg/kg (N=38)***	***All TCZ (N=75)***
JIA ACR30 Response				
N	37	37	38	75
Responder, N (%)	9 (24)	31 (84)	37 (97)	68 (91)
95% C.I.	(11, 38)	(72, 96)	(92, 100)	(84, 97)
Weighted difference vs. Placebo		61	72	67
95% C.I.		(36, 86)	(51, 93)	(51, 83)
p-value		<0.0001	<0.0001	<0.0001
JIA ACR50 Response				
N	37	37	38	75
Responder, N (%)	4 (11)	29 (78)	35 (92)	64 (85)
95% C.I.	(1, 21)	(65, 92)	(84, 100)	(77, 93)
Weighted difference vs. Placebo		71	76	74
95% C.I.		(47, 95)	(54, 98)	(58, 90)
p-value		<0.0001	<0.0001	<0.0001
JIA ACR70 Response				
N	37	37	38	75
Responder, N (%)	3 (8)	25 (68)	28 (74)	53 (71)
95% C.I.	(0, 17)	(53, 83)	(60, 88)	(60, 81)
Weighted difference vs. Placebo		59	66	63
95% C.I.		(33, 84)	(44, 89)	(46, 80)
p-value		<0.0001	<0.0001	<0.0001
JIA ACR90 Response				
N	37	37	38	75
Responder, N (%)	2 (5)	13 (35)	15 (40)	28 (37)
95% C.I.	(0.0, 13)	(20, 51)	(24, 55)	(26, 48)
Weighted difference vs. Placebo		25	40	33
95% C.I.		(0, 51)	(18, 61)	(17, 50)
p-value		0.0487	0.0003	<0.0001

Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at baseline.
Source: primary_analysis.sas;

Figure 4: The Proportion of JIA ACR30 Responders with Absence of Fever and JIA ACR30/50/70/90 Responders at Week 12 (ITT)

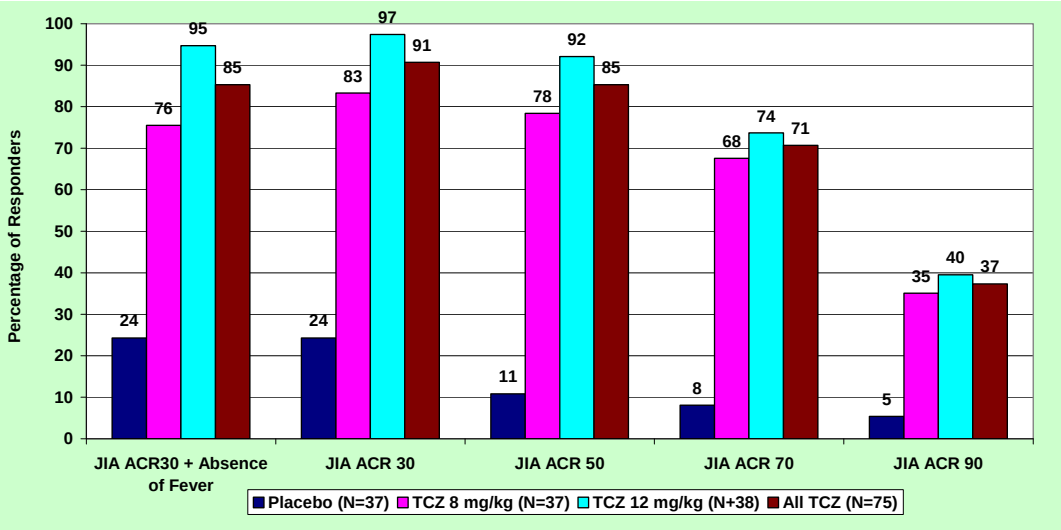
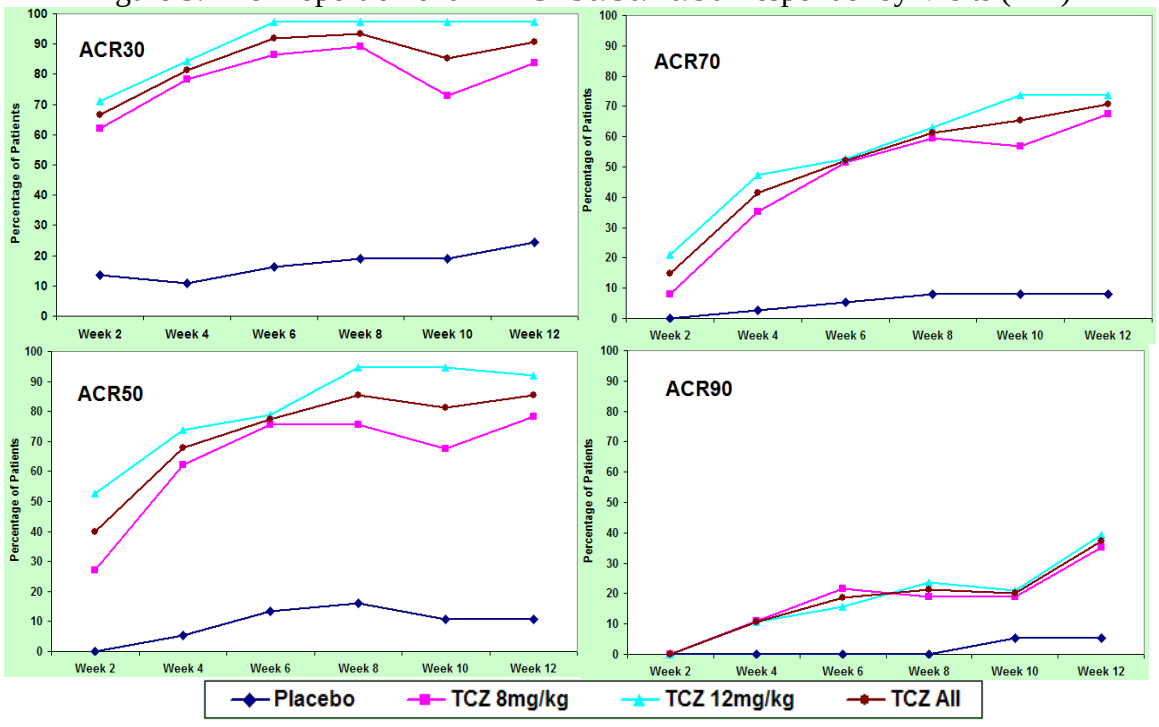


Figure 5: The Proportion of JIA ACR30/50/70/90 Responder by Visits (ITT)



During the Part II, a 92-week, single-arm, open-label extension, the patients treated with TCZ maintain the JIA ACR30 responds. As shown in Figure 6 and Figure 7, the TCZ 8mg/kg and 12 mg/kg have similar response rate of the JIA ACR30 response with absence of fever and JIA ACR30/50/70/90 response beyond week 12.

Figure 6: The Proportion of JIA ACR30 Responders with Absence of Fever beyond Week 12

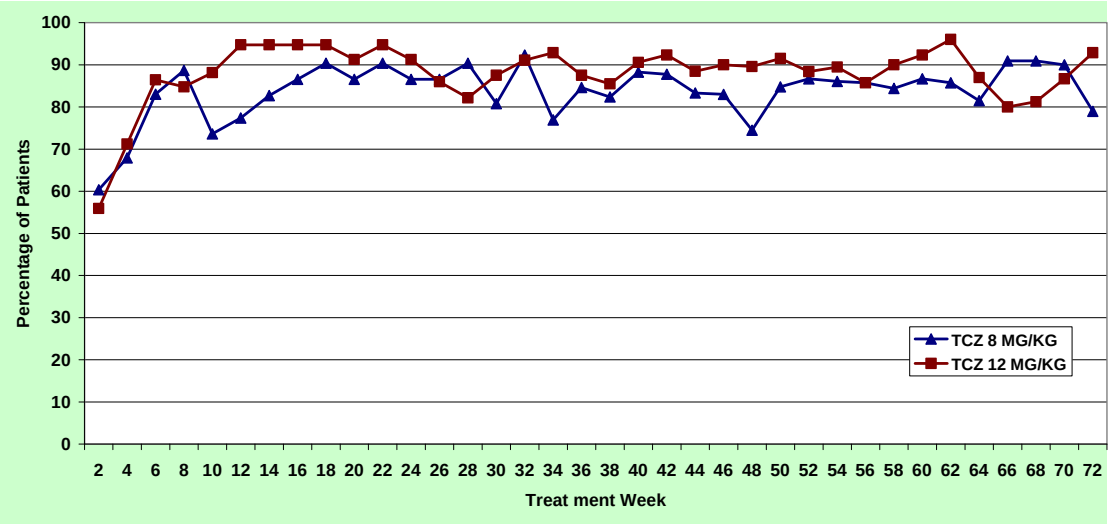
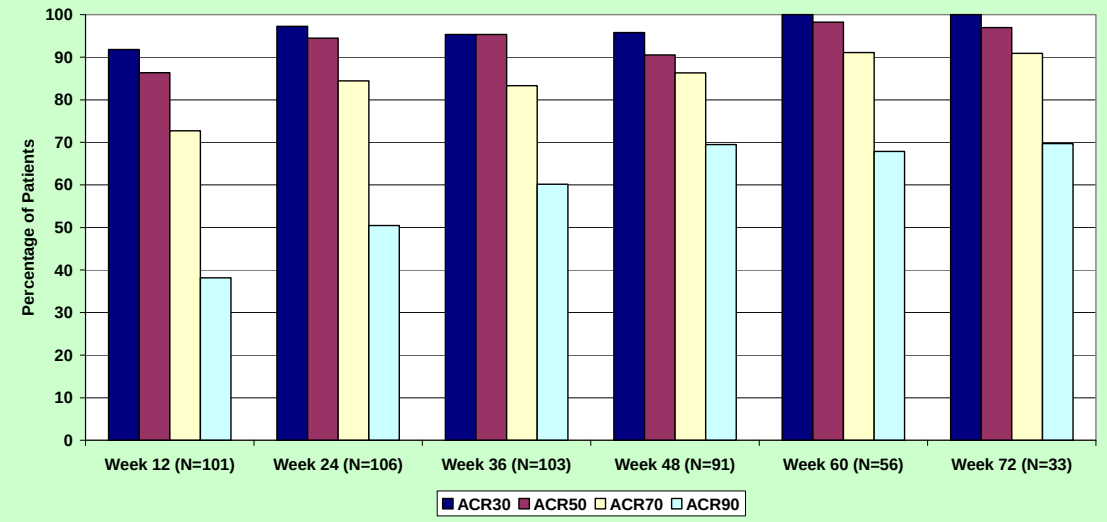


Figure 7: The Proportion of JIA ACR30/50/70/90 Responders beyond Week 12



JIA ACR Core Set Components

The JIA ACR core set that determines the JIA ACR response includes the number of active joints, number of joints with limitation of movement, parent global assessment VAS, physician global assessment VAS, CHAQ-DI score, and ESR.

The sponsor's analysis of variance of the percent change from baseline in the JIA ACR core set components at week 12 adjusting for treatment and the randomization stratification factors applied at baseline is shown in Table 9 . Patients who withdrew, received escape medication, or for whom the endpoint could not be determined were excluded in this analysis. I performed the same analysis based on the ITT population using LOCF imputation (Table 10). There were total

of 21 patients who had the missing JIA ACR Core set components at week 12; 95% of them treated with placebo and the missing were due to the lack of efficacy (escape to TCZ treatment). Therefore, in my opinion, the LOCF imputation method was reasonable in this situation. The two analyses bring to the same result which shows the TCZ treated patients significantly improved the all JIA CAR Core set components at week 12.

Figure 8 displays the line plot of percent change from baseline of JIA ACR core set components based on the observed data. Compared to placebo, both TCZ doses treated patients had a higher improvement. The TCZ 12mg/kg/day treated patients had steady improvement than TCZ 8mg/kg/day treated patients.

Table 9: Percent Change from Baseline in the JIA ACR Core Set Components at Week 12 (Observed)

Observed Data		***Placebo (N=37)***	***TCZ 8 mg/kg (N=37)***	***TCZ 12 mg/kg (N=38)***	***All TCZ (N=75)***
Joints with active arthritis (0-71)					
N		17	37	36	73
Baseline	Mean (STD)	16.9 (12.9)	23.5 (16.6)	19.2 (15.2)	21.3 (15.9)
At Week 12	Mean (STD)	9.5 (9.0)	10.6 (16.0)	4.1 (3.4)	7.3 (11.9)
Weighted difference in % Change			-39.4	-29.0	-33.4
95% C.I.			(-69.8, -9.1)	(-55.1, -2.9)	(-53.2, -13.6)
p-value			0.012	0.030	0.001
Joints with limitation of movement (0-67)					
N		17	37	36	73
Baseline	Mean (STD)	17.9 (15.9)	23.4 (16.9)	18.1 (14.6)	20.7 (15.9)
At Week 12	Mean (STD)	14.4 (12.8)	14.1 (17.6)	6.5 (6.6)	10.3 (13.6)
Weighted difference vs. Placebo			-40.3	-19.3	-28.2
95% C.I.			(-77.6, -3.1)	(-51.3, 12.8)	(-52.6, -3.8)
p-value			0.034	0.235	0.024
Patient/parent global assessment of disease activity VAS					
N		17	37	36	73
Baseline	Mean (STD)	56.3 (21.2)	61.3 (22.8)	59.3 (25.0)	60.3 (23.8)
At Week 12	Mean (STD)	45.0 (26.0)	24.7 (22.7)	16.6 (20.2)	20.6 (21.7)
Weighted difference in % Change			-70.7	-59.8	-64.4
95% C.I.			(-106.1, -35.3)	(-90.2, -29.4)	(-87.5, -41.3)
p-value			<0.001	<0.001	<0.001
Physician global assessment of overall well-being VAS					
N		17	37	36	73
Baseline	Mean (STD)	61.4 (21.1)	68.1 (15.1)	71.1 (16.2)	69.6 (15.7)
At Week 12	Mean (STD)	34.8 (27.2)	24.9 (23.9)	17.6 (12.5)	21.2 (19.2)
Weighted difference in % Change			-27.5	-29.3	-28.5
95% C.I.			(-51.6, -3.3)	(-50.1, -8.5)	(-44.3, -12.8)
p-value			0.027	0.006	<0.001
CHAQ-DI score					
N		17	37	36	73
Baseline	Mean (STD)	1.7 (0.8)	1.7 (0.8)	1.8 (0.8)	1.7 (0.8)
At Week 12	Mean (STD)	1.3 (1.0)	1.0 (0.8)	0.9 (0.7)	0.9 (0.8)
Weighted difference in % Change			-38.8	-30.8	-34.5
95% C.I.			(-79.3, 1.6)	(-67.7, 6.0)	(-61.7, -7.2)
p-value			0.060	0.100	0.014
ESR					
N		17	37	36	73
Baseline	Mean (STD)	54.1 (35.4)	50.9 (31.7)	64.1 (29.8)	57.6 (31.2)
At Week 12	Mean (STD)	38.7 (30.4)	4.1 (4.1)	2.9 (2.1)	3.5 (3.3)
Weighted difference in % Change			-75.9	-155.5	-121.8
95% C.I.			(-117.0, -34.9)	(-190.8, -120.2)	(-149.9, -93.7)

p-value			<0.001	<0.001	<0.001

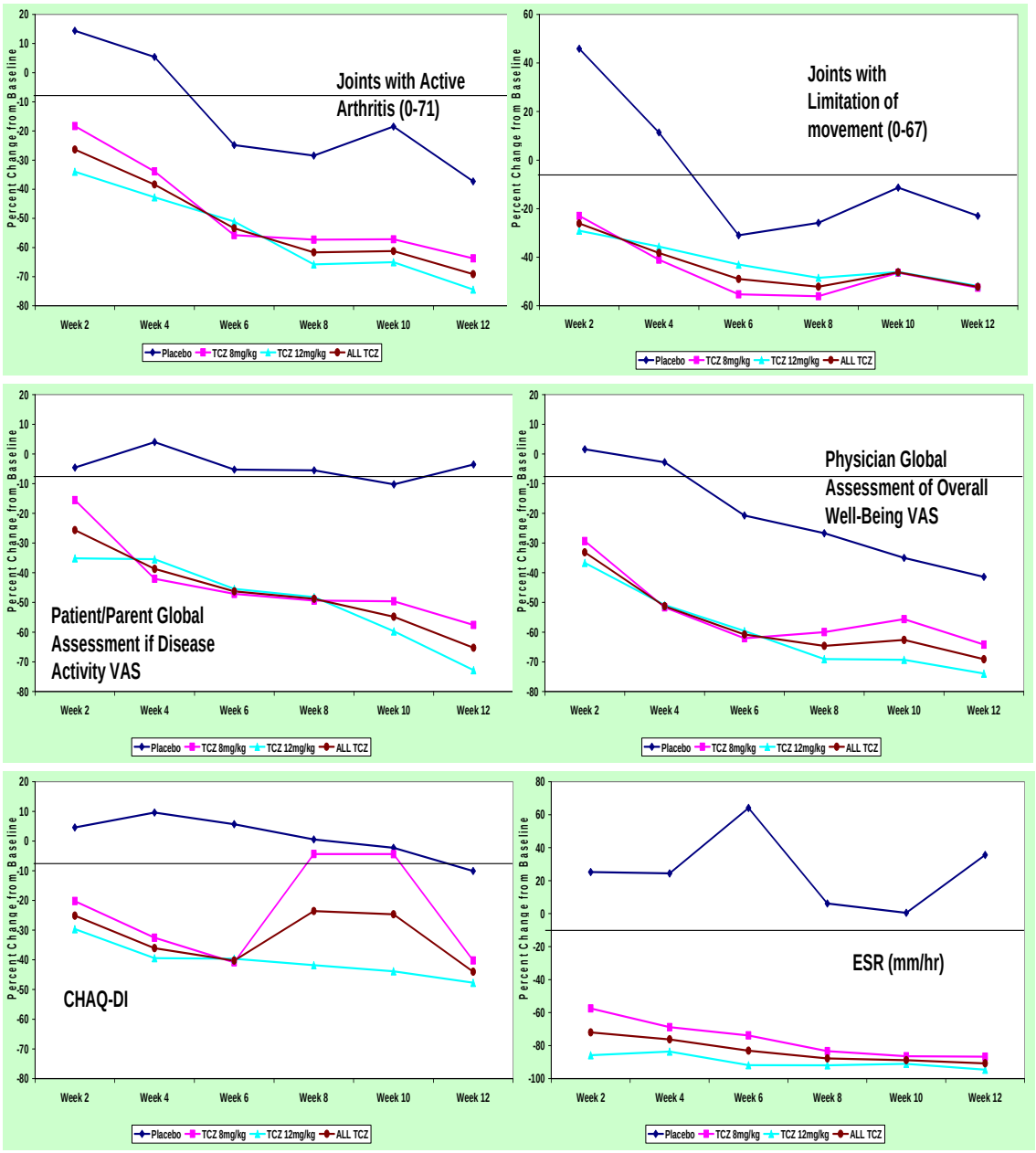
ANCOVA model adjusted for the randomization stratification factors applied at baseline. Source: secondary_analysis sas;

Table 10: Percent Change from Baseline in the JIA ACR Core Set Components at Week 12 (LOCF Imputed)

LOCF Imputation Applied		***Placebo (N=37)***	***TCZ 8 mg/kg (N=37)***	***TCZ 12 mg/kg (N=38)***	***All TCZ (N=75)***
Joints with active arthritis (0-71)					
N		37	38	37	75
Baseline	Mean (STD)	16.9 (12.9)	23.5 (16.6)	19.2 (15.2)	21.3 (15.9)
At Week 12	Mean (STD)	16.7 (14.5)	11.2 (16.2)	4.1 (3.4)	7.6 (12.1)
Weighted difference in % Change			-74.6	-66.8	-70.4
95% C.I.			(-107.5, -41.7)	(-96.8, -36.8)	(-92.3, -48.6)
p-value			<0.001	<0.001	<0.001
Joints with limitation of movement (0-67)					
N		37	38	37	75
Baseline	Mean (STD)	17.9 (15.9)	23.4 (16.9)	18.1 (14.6)	20.7 (15.9)
At Week 12	Mean (STD)	18.2 (14.9)	14.5 (17.5)	6.4 (6.5)	10.4 (13.6)
Weighted difference vs. Placebo			-77.1	-95.0	-86.6
95% C.I.			(-140.2, -13.9)	(-152.6, -37.5)	(-128.9, -44.8)
p-value			0.017	0.001	<0.001
Patient/parent global assessment of disease activity VAS					
N		37	38	37	75
Baseline	Mean (STD)	56.3 (21.2)	61.3 (22.8)	59.3 (25.0)	60.3 (23.8)
At Week 12	Mean (STD)	56.8 (26.7)	25.9 (23.6)	17.9 (21.4)	21.8 (22.6)
Weighted difference in % Change			-77.5	-65.5	-71.0
95% C.I.			(-103.1, -52.0)	(-88.9, -42.4)	(-88.1, -53.9)
p-value			<0.001	<0.001	<0.001
Physician global assessment of overall well-being VAS					
N		37	38	37	75
Baseline	Mean (STD)	61.4 (21.1)	68.1 (15.1)	71.1 (16.2)	69.6 (15.7)
At Week 12	Mean (STD)	56.4 (31.0)	25.6 (24.2)	18.5 (13.4)	22.1 (19.7)
Weighted difference in % Change			-51.5	-55.1	-53.5
95% C.I.			(-70.5, -32.5)	(-72.4, -37.8)	(-66.1, -40.8)
p-value			<0.001	<0.001	<0.001
CHAQ-DI score					
N		37	38	37	75
Baseline	Mean (STD)	1.7 (0.8)	1.7 (0.8)	1.8 (0.8)	1.7 (0.8)
At Week 12	Mean (STD)	1.6 (1.0)	1.0 (0.9)	0.9 (0.7)	1.0 (0.8)
Weighted difference in % Change			-72.0	-42.1	-55.7
95% C.I.			(-111.5, 32.5)	(-78.1, 6.1)	(-82.1, -29.2)
p-value			0.005	0.022	<0.001
ESR					
N		37	38	37	75
Baseline	Mean (STD)	54.1 (35.4)	50.9 (31.7)	64.1 (29.8)	57.6 (31.2)
At Week 12	Mean (STD)	60.6 (39.6)	4.0 (4.1)	4.7 (11.1)	4.4 (8.3)
Weighted difference in % Change			-111.6	-143.3	-128.9
95% C.I.			(-149.5, -73.7)	(-177.8, -108.7)	(-154.3, -103.5)
p-value			<0.001	<0.001	<0.001

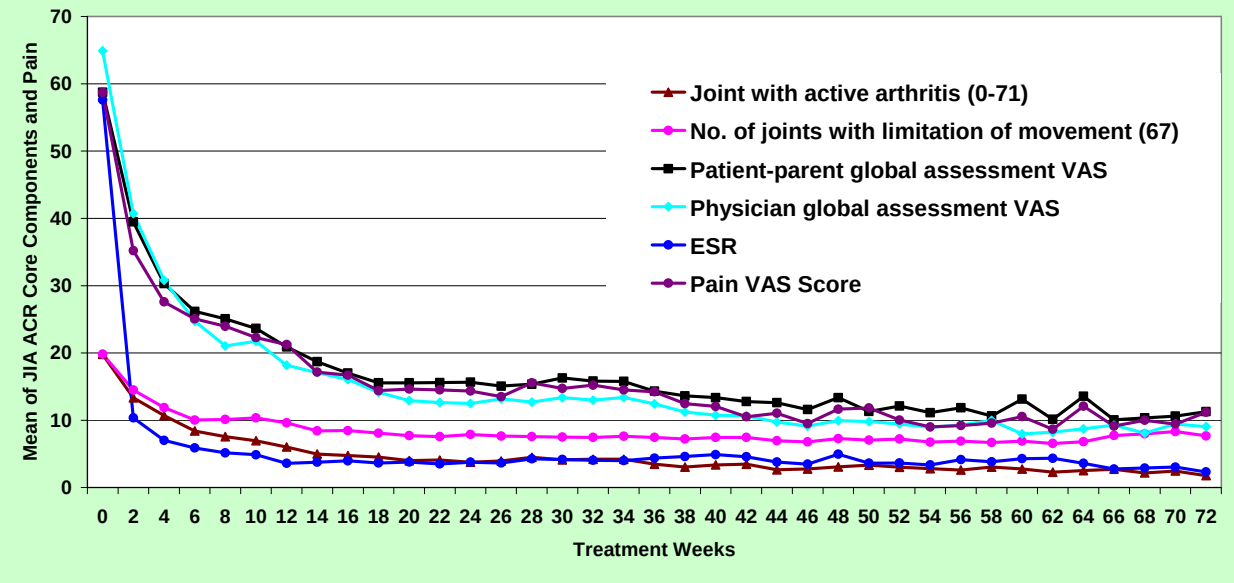
ANCOVA model adjusted for the randomization stratification factors applied at baseline.
The LOCF rule was applied to the missing JIA ACR core set components at week 12. Source: secondary_analysis.sas;

Figure 8: Line Plot of Percent Change from Baseline in JIA ACR Core Set Components (Observed Data)



During the Part II, a 92-week, single-arm, open-label extension, Figure 9 descriptively shows that the JIA ACR core component values continue to decrease beyond the week 12 and appears to maintain at certain levels after week 18. Of note, there was only about 100 patient at week 44 and only 30 patient by week 72.

Figure 9: The Mean Score of JIA ACR Core Components and Pain VAS beyond Week 12
(ITT – combined tocilizumab 12mg/kg and 8mg/kg)



Systemic Features

Table 11 displays the analysis results for systemic features including fever, rash, and pain at week 12. If systemic features could not be determined due to insufficient amount of diary data or received escape medication then it was assumed present. Forty-one (55%) of the TCZ patients and 24 (65%) placebo patients had fever at baseline. Of those patients with fever at baseline, 35 (85%) TCZ patients and five (21%) placebo patients were free of fever at week 12. Eighteen (49%) placebo patients and 22 (29%) TCZ patients had rash at baseline. Of those patients with rash at baseline, 14 (64%) TCZ patients and two (11%) placebo patients were free of rash at week 12.

Fifty-eight TCZ patients and seven placebo patients had a minimally important improvement defined by the sponsor of at least 0.13 in CHAQ-DI score from baseline to week 12. Patients who achieved this improvement included 77% of the TCZ patients in contrast to 19% of the placebo patients. (Table 11)

The adjusted mean in absolute change from baseline in the pain VAS score at week 12 was different in the patients treated with TCZ compared to those treated with placebo (TCZ-placebo = -41.6). (Table 11)

During the Part II, a 92-week, single-arm, open-label extension, Figure 10 and Figure 11 descriptively shows that response rate for the CHAQ-DI score and systemic feature continue to decrease beyond the week 12 and appear to maintain at certain levels. Of note, there was about 100 patients at week 44 and only about 30 patients by week 72.

Table 11: The Systemic Features (ITT)

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
The proportion of patients with fever at baseline who are free of fever at week 12				
N	24	15	26	41
Responder	5 (20.8)	11 (73.3)	24 (92.3)	35 (85.4)
95% C.I.	(4.6, 37.1)	(51.0, 95.7)	(82.1, 100.0)	(74.5, 96.2)
Weighted difference vs. Placebo		54.8	71.6	65.3
95% C.I.		(14.3, 95.2)	(40.5, 102.7)	(40.6, 90.0)
p-value		0.008	<0.001	<0.001
The proportion of patients with rash at baseline who are free of rash at week 12				
N	18	9	13	22
Responder	2 (11.1)	4 (44.4)	10 (76.9)	14 (63.6)
95% C.I.	(0.0, 25.6)	(12.0, 76.9)	(54.0, 99.8)	(43.5, 83.7)
Weighted difference vs. Placebo		12.9	86.0	52.1
95% C.I.		(-35.9, 61.7)	(48.0, 124.0)	(21.6, 82.5)
p-value		0.605	<0.001	<0.001
Analysis of Variance of Absolute Change from Baseline in the Pain VAS at Week 12 (LOCF)				
N	37	38	37	75
Baseline Mean (STD)	53.5 (22.4)	60.7 (24.4)	62.1 (23.9)	61.4 (24.0)
At Week 12 Mean (STD)	54.4 (28.7)	26.1 (25.6)	19.0 (22.8)	22.5 (24.3)
LS Mean difference in Change		-40.1	-41.0	-40.6
95% C.I.		(-55.9, -24.3)	(-55.4, -26.6)	(-51.1, -30.1)
p-value		<0.001	<0.001	<0.001
The proportion of patients with minimally important improvement in CHAQ-DI Score at week 12				
N	37	37	38	75
Responder	7 (18.9)	26 (70.3)	32 (84.2)	58 (77.3)
95% C.I.	(6.3, 31.5)	(55.5, 85.0)	(72.6, 95.8)	(67.9, 86.8)
Weighted difference vs. Placebo		46.8	63.9	56.3
95% C.I.		(21.4, 72.2)	(41.8, 86.1)	(39.6, 73.0)
p-value		<0.001	<0.001	<0.001

Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at baseline.
Source: secondary_analysis.sas;

Figure 10: The Mean of CHAQ-DI Score beyond Week 12
(ITT – combined tocilizumab 12mg/kg and 8mg/kg)

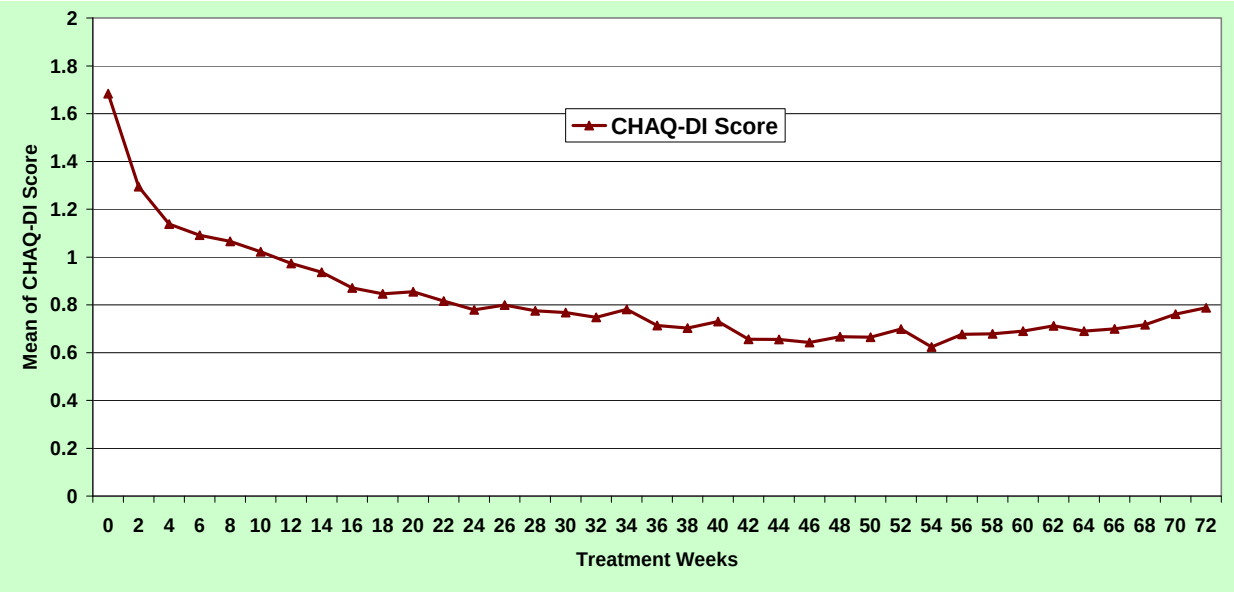
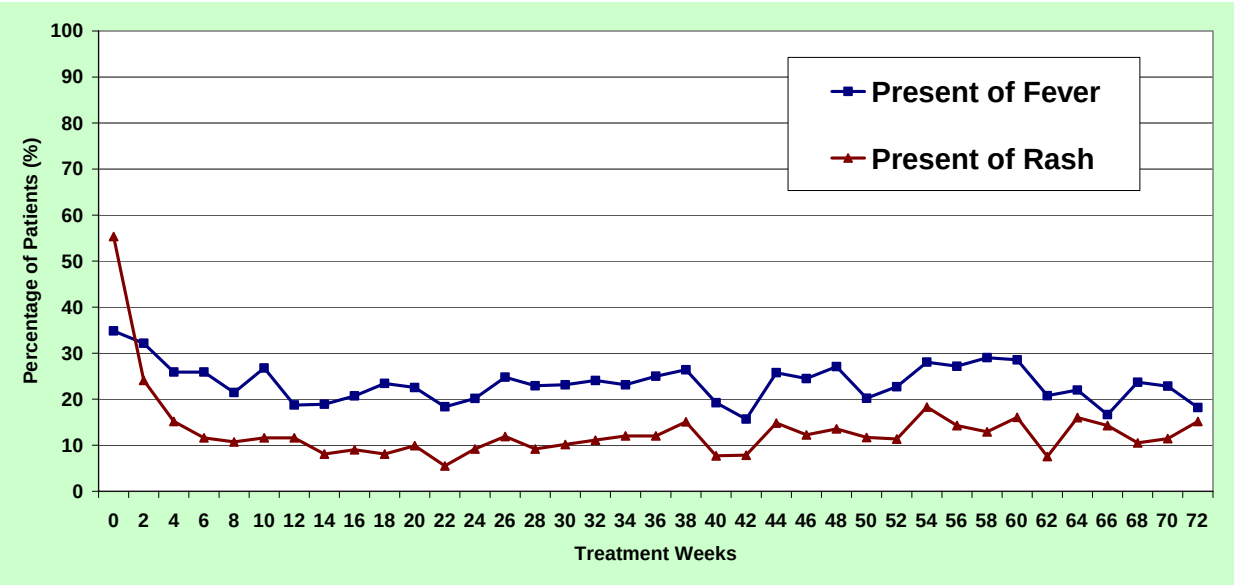


Figure 11: The Systemic Features Responders beyond Week 12
(ITT – combined tocilizumab 12mg/kg and 8mg/kg)



Reduction in Corticosteroid Dose

The sponsor evaluated secondary endpoints in both Part I and Part II of the study pertaining to the reduction in corticosteroid dose. As shown in Table 12, of the 31 placebo and 70 TCZ patients receiving OCS at baseline, one (3%) placebo and 17 (24%) TCZ patients achieved a JIA ACR70 response at week 6 or 8 enabling reduce OCS dose by ≥20% without subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12. The result of ANCOVA analysis shows that TCZ 8mg/kg treated patients had less reduction of OCS use during the first 12 weeks.

Of note, TCZ 8mg/kg treated patients started with much lower OCS dose compared with other two treatment groups (Figure 12).

During the Part II, from week 12 onward, concomitant OCS doses decreased over time (Figure 12). Of the 103 patients who used OCS at baseline. 87% of them had reduced the OCS dose and 2% stop the OCS use by week 12. By week 44, only 44 (out of the 91 patients) remained in the trial and 48% of them were off OCS use and 48% reduced the OCS dose (Table 13).

Table 12: Oral Corticosteroid Dose Tapering

	Placebo (N=37)	***TCZ 8 mg/kg (N=37)***	***TCZ 12 mg/kg (N=38)***	***All TCZ (N=75)***
The proportion of patients receiving OCS at baseline and JIA ACR70 response at week 6/8 who reduced OCS dose by ≥20% without subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12				
N	31	34	36	70
Responder	1 (3.2)	8 (23.5)	9 (25.0)	17 (24.3)
95% C.I.	(0.0, 9.4)	(9.3, 37.8)	(10.9, 39.1)	(14.2, 34.3)
Weighted difference vs. Placebo		22.2	19.2	20.3
95% C.I.		(-7.3, 51.7)	(-3.8, 42.1)	(2.2, 38.4)
p-value		0.140	0.101	0.0280
The proportion of patients receiving OCS at baseline reduced OCS dose during12 weeks treatment				
N	31	34	36	70
Responder (Responder Rate)	1 (3.2)	14 (41.2)	18 (50.0)	32 (45.7)
95% C.I. of responder rate	(0.0, 9.4)	(24.6, 57.7)	(33.7, 66.3)	(34.0, 57.4)
Weighted difference vs. Placebo		38.8	41.3	40.4
95% C.I.		(8.9, 68.8)	(17.8, 64.7)	(21.9, 58.5)
p-value		0.011	<0.001	<0.001
Analysis of Variance of Absolute Change from Baseline in the OCS Use at Week 12 (LOCF)				
N	37	38	38	75
Baseline Mean (STD)	0.27 (0.17)	0.21 (0.15)	0.36 (0.17)	0.29 (0.18)
At Week 12 Mean (STD)	0.26 (0.18)	0.19 (0.12)	0.29 (0.15)	0.24 (0.14)
Weighted difference in Change		-0.013	-0.069	-0.05
95% C.I.		(-0.07, 0.04)	(-0.11, -0.03)	(-0.08, -0.01)
p-value		0.617	0.002	0.008

Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at baseline.
Source: secondary_analysis.sas;

Figure 12: Summary of Intakes of Oral Corticosteroid Treatment (mg/kg/day) by Visit and Treatment (ITT)

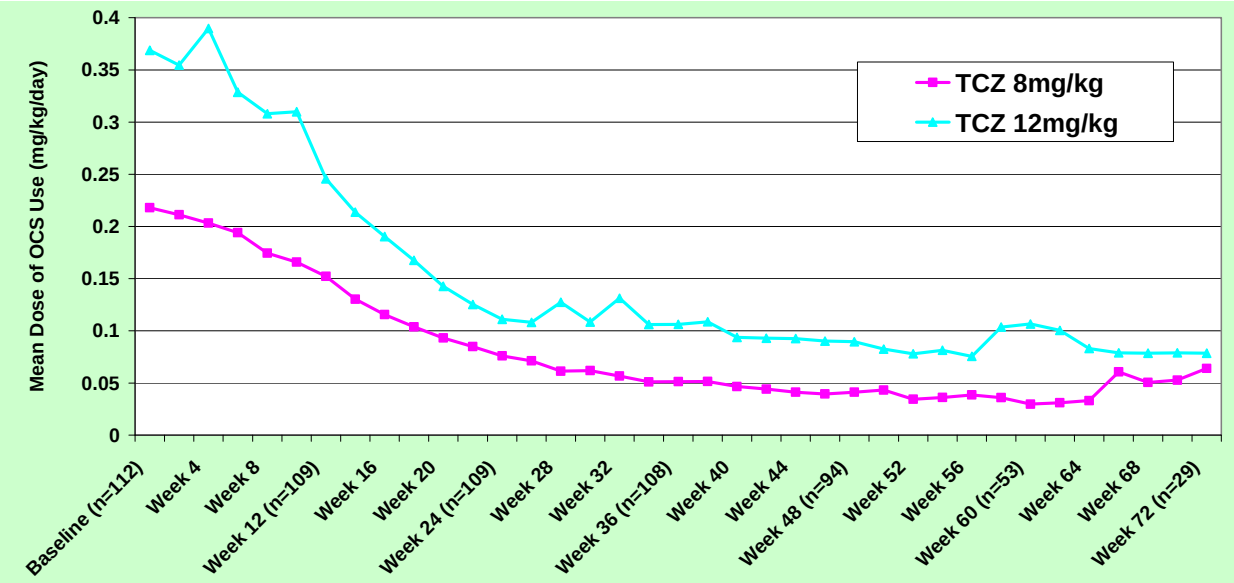


Table 13: Summary of Change of Oral Corticosteroid Treatment by Visit and Treatment (ITT)

	TCZ 8 mg/kg (N=46) N (%)					*TCZ 12 mg/kg (N=55) N (%)*				
Week	N	Increased	Unchanged	Decreased	Stopped	N	Increased	Unchanged	Decreased	Stopped
12	45	5 (11)	0	40 (89)	0	55	6 (11)	0	47 (85)	2 (4)
16	45	1 (2)	0	43 (96)	1 (2)	55	0	1 (2)	51 (93)	3 (5)
20	45	3 (7)	0	35 (78)	7 (16)	55	0	0	45 (82)	10 (18)
24	45	2 (4)	0	34 (76)	9 (20)	55	0	0	42 (76)	13 (24)
28	45	2 (4)	0	27 (60)	16 (36)	54	1 (2)	0	36 (67)	17 (32)
32	45	2 (4)	0	24 (53)	19 (42)	54	1 (2)	0	34 (63)	19 (35)
36	45	2 (4)	0	23 (51)	20 (44)	54	0	0	32 (59)	22 (41)
40	43	2 (5)	0	21 (49)	20 (47)	51	0	0	27 (53)	24 (47)
44	41	2 (5)	0	17 (42)	22 (54)	50	1 (2)	0	27 (54)	22 (44)
48	41	2 (5)	0	16 (39)	23 (56)	46	1 (2)	0	25 (54)	20 (44)
52	40	1 (3)	0	15 (38)	24 (60)	38	0	0	22 (58)	16 (42)
56	31	1 (3)	0	13 (42)	17 (54)	32	0	0	17 (53)	15 (47)
60	24	0	0	9 (38)	15 (62)	24	0	0	15 (63)	9 (37)
64	19	1 (5)	0	5 (26)	13 (68)	22	0	0	13 (59)	9 (41)
68	19	2 (1.1)	0	5 (26)	12 (63)	16	0	0	8 (50.0)	8 (50.0)
72	16	2 (13)	0	5 (31)	9 (56)	13	0	0	6 (46)	7 (54)

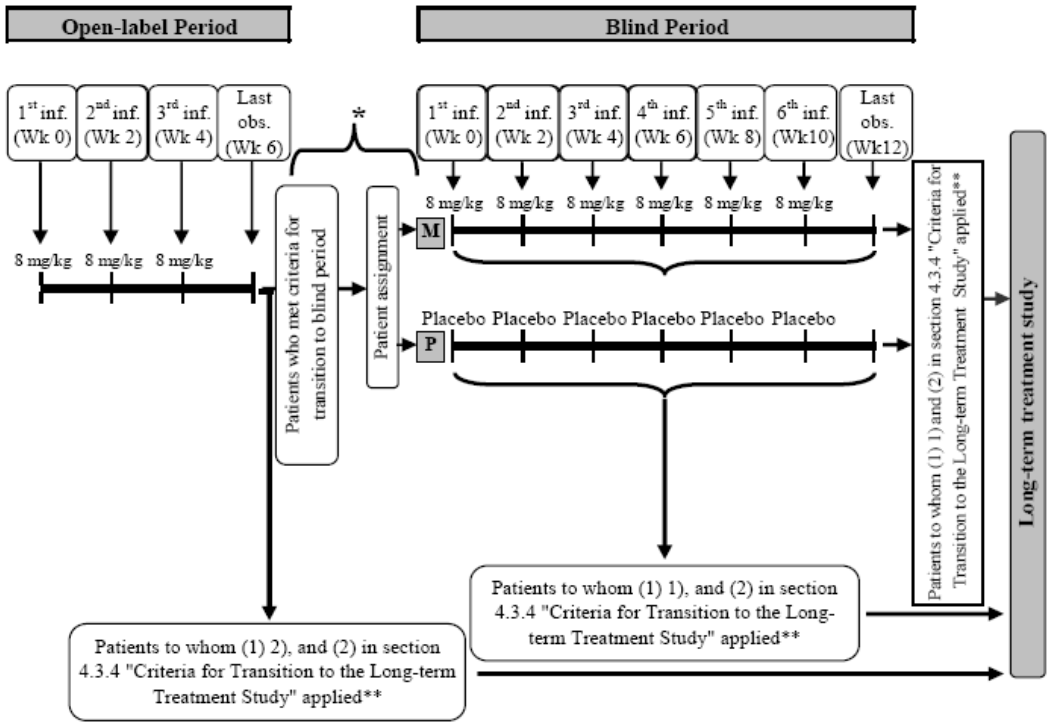
3.2 Evaluation of Efficacy Study MRA216JP

Study MRA316JP was conducted in 8 centers in Japan during the year 2004 and 2005. As show in Figure 13, study MRA316JP was a phase 3, dual-phase (open-label and blind phase) study in pediatric patients aged 2 to 19 years old with sJIA (under 16 years of age at onset) in Japan who failed to respond adequately to corticosteroid treatment for ≥3 months at a dose of ≥0.2 mg/kg as prednisolone equivalent. It comprised an initial 6-week open-label phase assessing the efficacy, safety, and pharmacokinetics of TCZ in 56 children with sJIA receiving TCA, 8 mg/kg every 2 weeks by intravenous infusion for 6 weeks (i.e., three doses in total). Patients who responded to TCZ in this open-label induction portion (i.e., achieved at least a JIA ACR30 response and CRP of <0.5 mg/dL on the last observation day) entered the double-blind portion of the study and

were randomized to receive placebo (23 patients) or 8 mg/kg TCZ (21 patients) every two weeks for 12 weeks (i.e., six doses in total).

The primary efficacy analysis was based on the full analysis set (FAS) for both open and blinded period. The FAS was defined as all ITT patients except 1) untreated patients 2) patients with main eligibility criteria violations 3) non-monitored patients (i.e., whom the measured values for the primary variables could not be used).

Figure 13: MRA316JP Study Design



Efficacy Endpoints:

During the Open-label period, primary endpoints was the percentage of patients achieved ACR30 and percentage of patients achieved CRP<0.5 mg/dL on the last observation day. The secondary endpoints were:

i. Time courses of CRP and ESR up to the last observation day
ii. Time courses of percentage of patients achieved ACR30/50/70 up to the last observation day
iii. Time courses of the JIA core set variables up to the last observation day
iv. Time course of pain (visual analogue scale) up to the last observation day
v. Time course of maximum body temperature up to the last observation day
vi. Time course of systemic feature score up to the last observation day

During the blinded period, the primary endpoint was the rate of maintained responder rate (percentage of patients completed the 12 weeks without needing rescue medication. The criteria

for rescue were if either patients had a CRP value of ≥0.5 mg/dL or did not achieve a JIA ACR30 response). The secondary endpoints were as same as the open-label period.

The treatment comparison was done using the $\chi 2$ test (exact) based on FAS population. A two-tailed significance level of 5% was used for hypothesis testing.

Assume the rates of maintained response were 60% in TCZ group and 10% in placebo group, the 20 patients per group (40 patients in total) would have 90% of power to detect a significant difference in the rate of maintained response between the placebo and TCZ group by $\chi 2$ test (exact) (a two-tailed significance level of 5%). Since it was estimated that 90% of these patients would move from the open-label period to the blind period, the final target number of patients for the present study was set at 45.

There was no major change to the Statistical Analysis Plan (SAP).

Patient Disposition, Demographic and Baseline Characteristics

In the open-label period, 56 patients were enrolled and all received the investigational product. Among these 56 patients, treatment was discontinued in 3 patients because anti-MRA antibodies appeared, in 2 patients because adverse events occurred and in 1 patient because the response was inadequate. As shown in Table 14, a total of 50 patients completed the open-label period and 44 patients who satisfied the criteria for transition moved to the blind period. One patient for whom blinding could not be maintained was excluded from the FAS population.

Table 14: Patients' Accountability N (%), (Core Population)

	Placebo	***TCZ8 mg/kg***	***Total***
Open label period			
Enrolled	--	--	56
Completed	--	--	50
Withdrawal	--	--	6
Double-Blind period			
Randomized	23	21	44
Completed (patients who were subjects of rescue)	22 (18)	19 (3)	41 (21)
Withdrawal	1 (<1)	2 (1)	3 (<1)
Reason of early discontinuation			
Adverse event	1 (<1)	1 (<1)	2 (<1)
Blinding could not be maintained	1 (<1)	0	1 (<1)
FAS population	23 (100)	20 (95)	43 (98)
PP population	23 (100)	19 (90)	42 (95)
Safety population	23 (100)	21 (100)	44 (100)

As shown in Table 15, the demographic and baseline disease characteristics were generally well balanced between the treatment groups in the blind period. Overall the mean age of the patient population was 8 years ranged from 2 to 19 years old. The age at onset of the underlying disease was 4.3 ± 2.6 (0.5 to 12.1) years and the disease duration was 4.5 ± 3.6 (0.4 to 16.2) years. The baseline ESR was 46.3 ± 24.3 (8 to 125) mm/hr and CRP was 5.7 ± 4.3 (1.6 to 19) mg/dL.
All patients had been treated previously with corticosteroids at a dose of 0.51 ± 0.36 (0.03 to 1.8) mg/kg as prednisolone equivalent (daily dose on the treatment start day). Thirty-six patients had

been previously treated with cyclosporin and 48 patients with methotrexate. Osteoporosis, cataract and glaucoma, considered to be attributable to corticosteroids, were also present in 34, 22 and 19 patients, respectively.

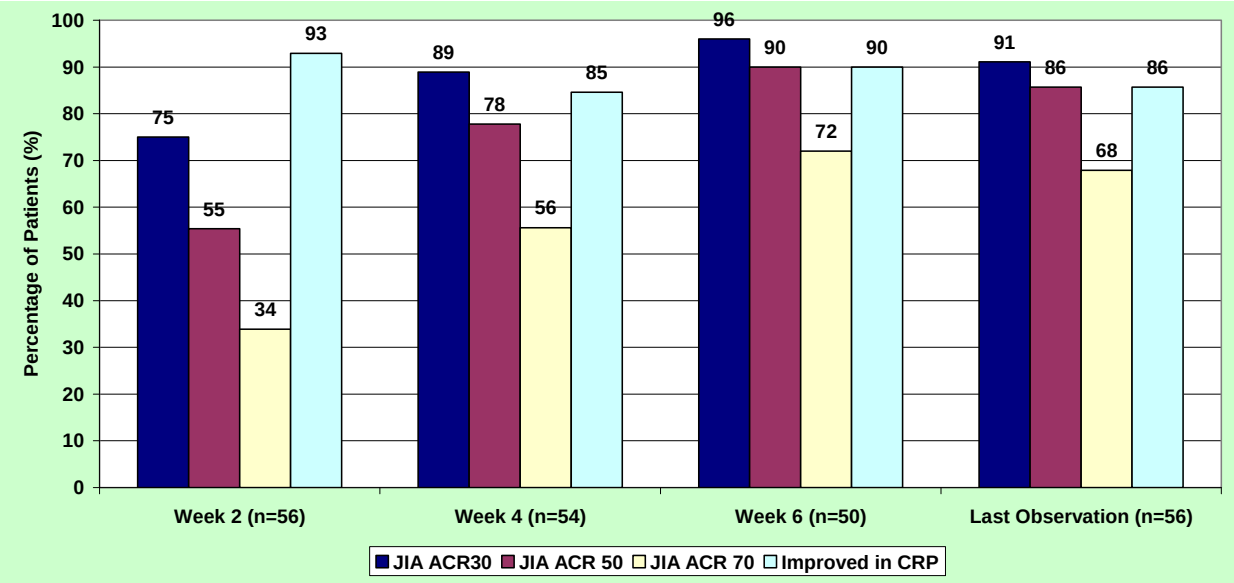
Table 15: Patients' Demographic and Baseline Characteristics N (%), (Blind Period, FAS)

	Blind Period Placebo (N=23)	***Blind Period 8 mg/kg (N=20)***	***Open Period (N=56)***
Age (yrs)			
2-5 years old, N (%)	5 (22)	9 (45)	20 (34)
6-12 years old, N (%)	12 (52)	10 (50)	19 (34)
13-19 years old, N (%)	6 (26)	1 (5)	17 (30)
Mean (SD)	9.3 (4.5)	8.0 (4.3)	8.3 (4.4)
Median (Range)	8.0 (2 – 19)	7.5 (2 – 19)	8.0 (2 – 19)
Sex, N (%)			
Female	15 (65)	13 (65)	35 (63)
Male	8 (35)	7 (35)	21 (37)
Body Weight (kg)			
< 30, N (%)	11 (48)	13 (65)	34 (61)
≥ 30, N (%)	12 (52)	7 (35)	22 (39)
Mean (SD)	31.6 (13.6)	26.8 (9.0)	27.9 (11.7)
Median (Range)	32.5 (9.4 – 71.9)	25.0 (13.5 – 41.9)	24.8 (9.4 – 71.9)
Height (cm)			
Mean (SD)	118.7 (20.6)	110.5 (16.8)	113.2 (18.8)
Median (Range)	117.1 (83.1 – 176.0)	112.3 (85.2 – 141.3)	114.2 (82 – 176)
BSA (m**2)			
Mean (SD)	0.99 (0.30)	0.87 (0.21)	0.91 (0.26)
Median (Range)	0.93 (0.46 – 1.87)	0.86 (0.56 – 1.23)	0.87 (0.46 – 1.88)
Duration of the JIA (yrs)			
Mean (SD)	4.7 (4.0)	4.6 (3.5)	4.5 (3.6)
Median (Range)	3.8 (0.6 – 16.2)	3.7 (0.7 – 14.3)	3.7 (0.4 – 16.2)
ESR (mm/hr)			
Mean (SD)	38.7 (16.2)	43.4 (25.0)	46.3 (24.3)
Median (Range)	35 (8 – 68)	39.5 (8 – 103)	44.5 (8 – 125)
CRP (mg/dL)			
Mean (SD)	4.9 (3.2)	5.0 (4.3)	5.7 (4.3)
Median (Range)	3.8 (1.7 – 13.1)	3.5 (1.6 – 19.0)	4.4 (1.6 – 19.0)

Results and Conclusions

During the open-label period, the percentage of patients showing 30% improvement (ACR30) was 91% (52 of 56 patients, 95%CI: 80%, 97%) and the percentage of patients showing improvement in CRP on the last observation day (number of patients, 95% CI) was 86% (48 of 56 patients, 74% to 94%). Both percentages were high (Figure 14). The TCZ treated also had higher ACR50 and ACR70 responder rates.

Figure 14: Percentage of Patients Showing Improvement in the JIA Core Set by visit (open-label period)



During the double-blind period, the rate of maintained response was defined as the percentage of patients who completed the study and to whom neither the withdrawal criteria nor the rescue criteria applied during 12 weeks of the blind period and the groups were compared using the χ^2 test (exact). The rate of maintained response (number of patients, 95% CI), was 17% (4 of 23 patients, 5% to 39%) in the placebo group and 80% (16 of 20 patients, 56% to 94%) in the MRA group; hence, the rate of maintained response was significantly higher in the MRA group (Table 16). In Figure 15, the left part displays the rate of maintained response and the right part display Kaplan-Meier curve of the time at which each patient became a subject of rescue was defined as the event, and patients who dropped out of the study because the withdrawal criteria applied or in whom response was maintained on the last day of observation were censored.

The percentages of patients showing 30%, 50% and 70% improvement in the JIA core set in the TCZ group were maintained at high levels throughout the blinded period. In the placebo group by contrast, the percentages decreased as the blinded period progressed (Figure 16). In TCZ group, both CRP and ESR remained low throughout the blinded period, but in the placebo group, CRP and ESR increased in many patients after the start of the blinded period. CRP and ESR on the last observation day in the TCZ group were both lower (Figure 17).

Other efficacy endpoints supported the primary efficacy results and confirmed that the symptoms of systemic JIA are improved by administration of TCZ 8 mg/kg every 2 weeks and that response appears to be maintained.

Table 16: Rate of Maintained response (Double-blind Period)

	Placebo (N=37)	***TCZ 8 mg/kg (N=37)***	***p-value***
N	23	20	
Responder (rate)	4 (17)	16 (80)	
95% C.I.	(5, 39)	(56, 94)	<0.001

Figure 15: Primary and Secondary Endpoints of Double-blind Period

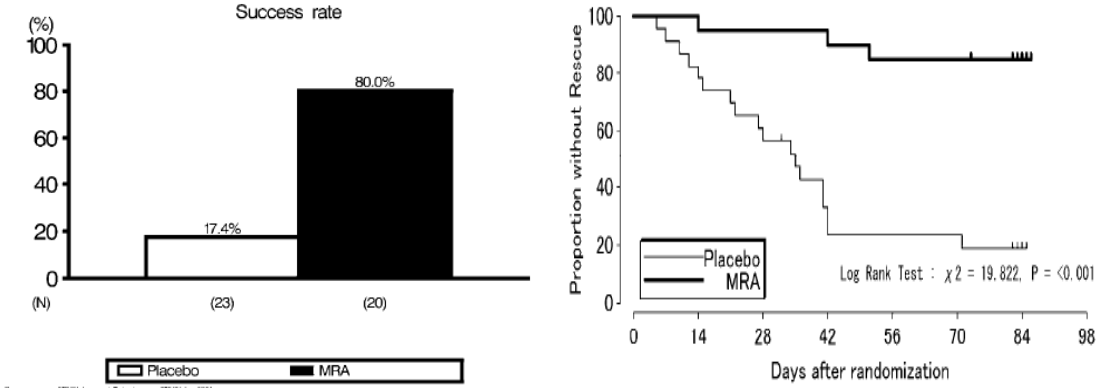


Figure 16: Proportion of JIA ACR30/50/70/90 Responder by Visits (ITT)

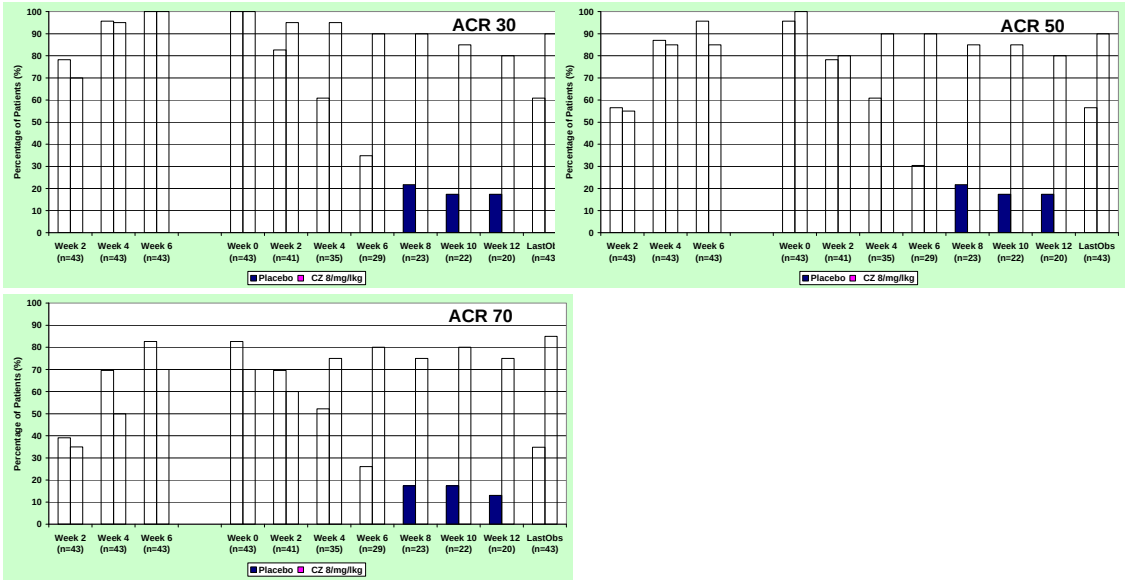
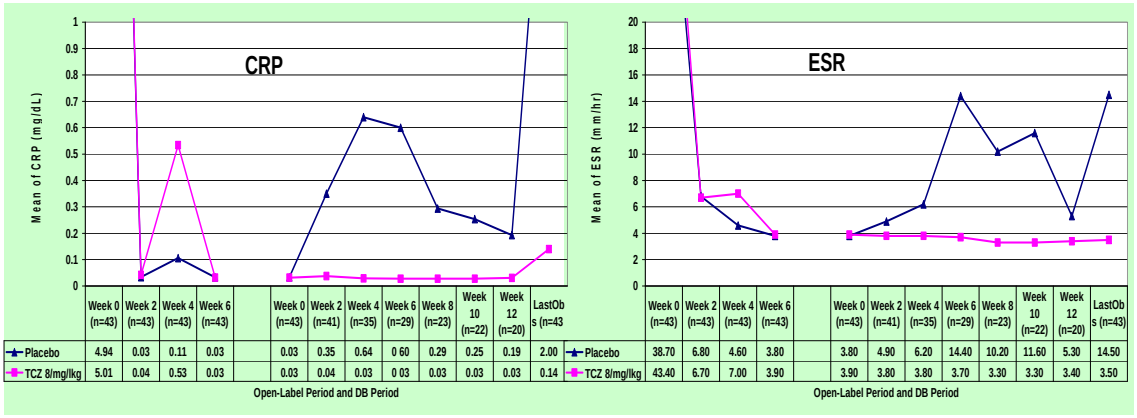


Figure 17: Mean of CRP and ESR by visit in both open-label and double-blind periods



	Week 0 (n=43)	Week 2 (n=43)	Week 4 (n=43)	Week 6 (n=43)		Week 0 (n=43)	Week 2 (n=41)	Week 4 (n=35)	Week 6 (n=29)	Week 8 (n=23)	Week 10 (n=22)	Week 12 (n=20)	LastObs (n=43
Placebo	4.94	0.03	0.11	0.03		0.03	0.35	0.64	0 60	0.29	0.25	0.19	2.00
TCZ 8/mg/lkg	5.01	0.04	0.53	0.03		0.03	0.04	0.03	0 03	0.03	0.03	0.03	0.14

	Week 0 (n=43)	Week 2 (n=43)	Week 4 (n=43)	Week 6 (n=43)		Week 0 (n=43)	Week 2 (n=41)	Week 4 (n=35)	Week 6 (n=29)	Week 8 (n=23)	Week 10 (n=22)	Week 12 (n=20)	LastObs (n=43)
Placebo	38.70	6.80	4.60	3.80		3.80	4.90	6.20	14.40	10.20	11.60	5.30	14.50
TCZ 8/mg/lkg	43.40	6.70	7.00	3.90		3.90	3.80	3.80	3.70	3.30	3.30	3.40	3.50

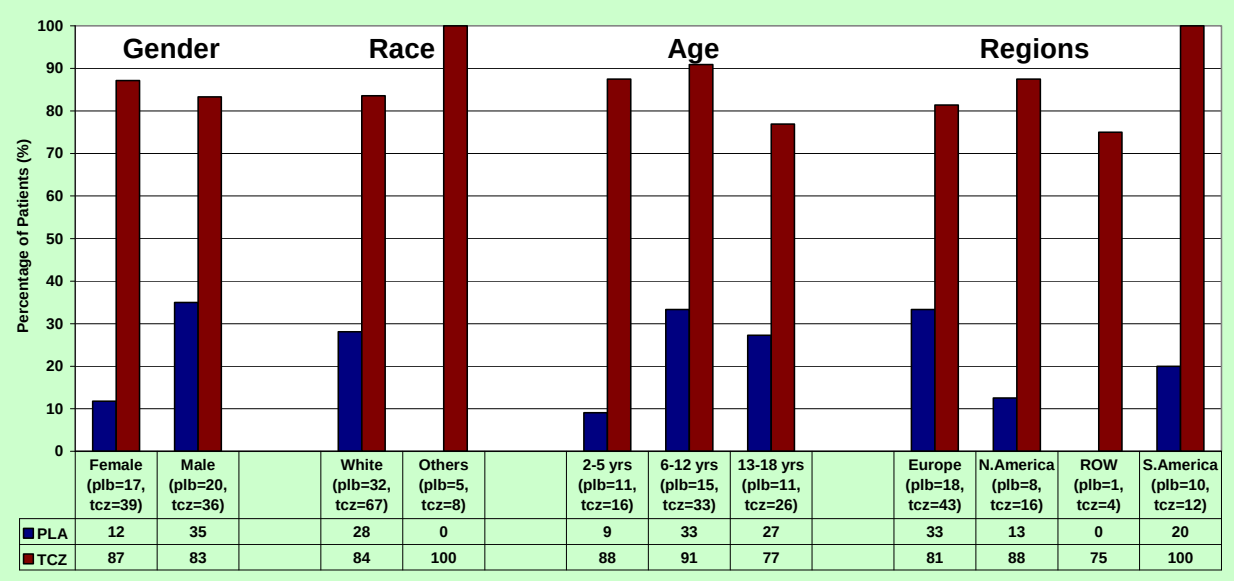
3.3 Evaluation of Safety

Dr. Kathleen Coyle, the Medical Reviewer, conducted the evaluation of the safety data separately. Reader is referred to Dr. Coyle's review for information regarding the safety profile of the drug.

4. FINDINGS IN SPECIFAL/SUBGROUP POPULATIONS

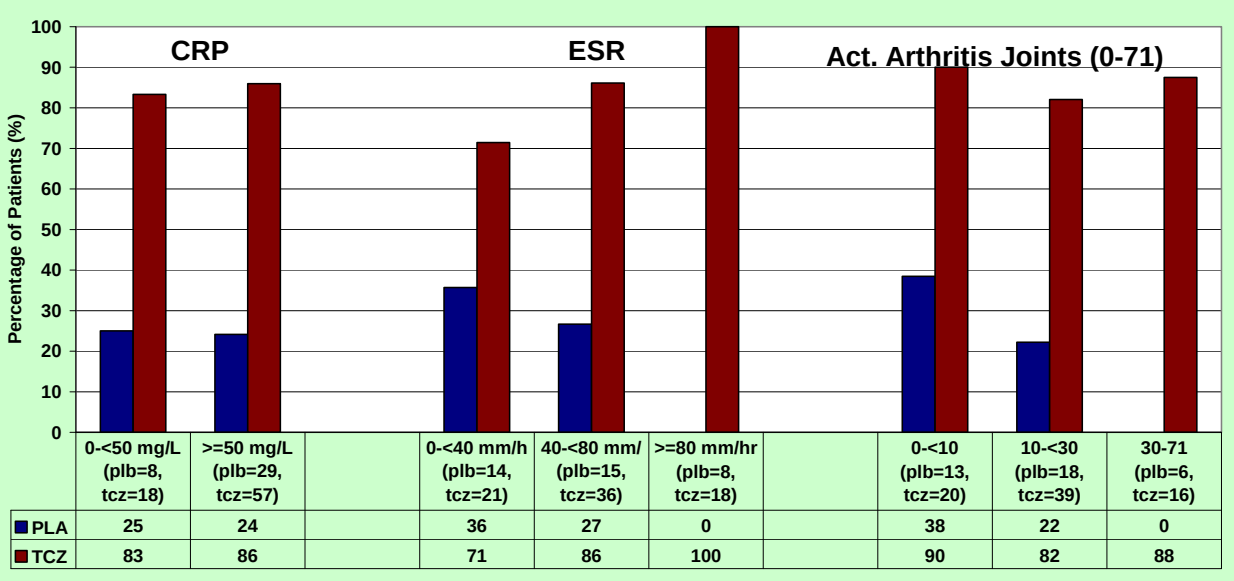
The summary of subgroup analysis on the primary efficacy endpoint in study WA18221 is given in Figure 18 and Figure 19. Interaction between treatment and subgroups were tested, there were significant interactions between treatment and baseline OCS use. The improvement by TCZ over placebo was smaller in patients who did not use OCS at baseline (40% in TCZ and 33% in placebo, respectively) than that in patients who used OCS at baseline (89% in TCZ and 23% in placebo, respectively). There is only small number of patients who did not use OCS; therefore the significant interaction can not be definitive.

Figure 18: Proportion of JIA ACR30 with Absence Fever at Week 12 by Demographic (ITT)

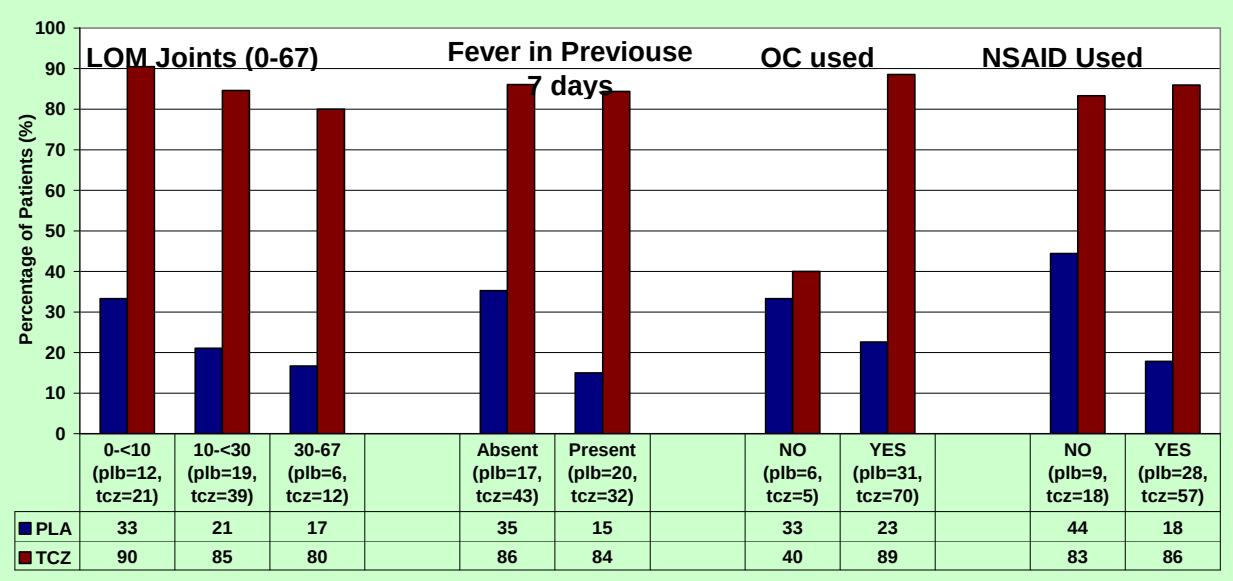


	Female (plb=17, tcz=39)	Male (plb=20, tcz=36)		White (plb=32, tcz=67)	Others (plb=5, tcz=8)		2-5 yrs (plb=11, tcz=16)	6-12 yrs (plb=15, tcz=33)	13-18 yrs (plb=11, tcz=26)		Europe (plb=18, tcz=43)	N.America (plb=8, tcz=16)	ROW (plb=1, tcz=4)	S.America (plb=10, tcz=12)
PLA	12	35		28	0		9	33	27		33	13	0	20
TCZ	87	83		84	100		88	91	77		81	88	75	100

Figure 19: Proportion of JIA ACR30 with Absence Fever at Week 12 by Baseline Characteristic



	0-<50 mg/L (plb=8, tcz=18)	>=50 mg/L (plb=29, tcz=57)		0-<40 mm/h (plb=14, tcz=21)	40-<80 mm/ (plb=15, tcz=36)	>=80 mm/hr (plb=8, tcz=18)		0-<10 (plb=13, tcz=20)	10-<30 (plb=18, tcz=39)	30-71 (plb=6, tcz=16)
PLA	25	24		36	27	0		38	22	0
TCZ	83	86		71	86	100		90	82	88



	0-<10 (plb=12, tcz=21)	10-<30 (plb=19, tcz=39)	30-67 (plb=6, tcz=12)		Absent (plb=17, tcz=43)	Present (plb=20, tcz=32)		NO (plb=6, tcz=5)	YES (plb=31, tcz=70)		NO (plb=9, tcz=18)	YES (plb=28, tcz=57)
PLA	33	21	17		35	15		33	23		44	18
TCZ	90	85	80		86	84		40	89		83	86

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There was no statistical issue identified during the review. The major efficacy findings are the following:

• The treatment effect of tocilizumab administrated through Intravenous Infusion every two weeks was measured by the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR30) with absence of fever (no temperature recording ≥ 37.5˚C in the preceding 7 days) after 12 weeks treatment. Eighty five percent (64/75) of the patients treated with tocilizumab and 24% (9/37) of placebo patients achieved this endpoint. Compared to placebo, the improvement by tocilizumab was 62% with a 95% CI of (45%, 78%), which was statistically significant and the improvement exceeded the MCID of 30%.

• Tocilizumab treated patients had a higher proportion of patients achieving JIA ACR30/50/70/90 responses at week 12 in comparison with the placebo patients. The improvement of tocilizumab in proportions of each JIA ACR response level was statistically significantly compared to placebo. This observed response rate were improved further following continued long-term treatment with tocilizumab.

• Positive effects were shown on joint inflammation, systemic effects, laboratory endpoints, and physical function in tocilizumab treated patients compared to patients treated with placebo.

• The mean concomitant oral corticosteroid dose during tocilizumab treatment decreased over time (>1 year). Over 94% of patients reduced their oral corticosteroid dose by LTE data cut (May 10th 2010).

5.2 Conclusions and Recommendations

Roche, proposes Actemra® injection for treatment of active Systemic Juvenile idiopathic Arthritis in patients 2 years of age and older. Based on evaluation of JIA ACR30 response with absence of fever after 12 weeks treatment, the applicant claims Actemra® is effective in improving JIA ACR30 response with absence of fever, reducing systemic features, and enabling corticosteroid dose reduction in sJIA patients; these effectiveness were maintained in the open labeling extension through 44 weeks of treatment. My review of the statistical evidence suggests support for the claim of improving JIA ACR30 response with absence of fever. Other efficacy endpoints support this main efficacy finding.

6. LABELING

Based on review of the submitted data, I have some comments and edits to the proposed label under Section 14.

(b) (4)

2 Pages of Draft Labeling have been withheld as b4 immediately following this page

SIGNATURES/DISTRIBUTION LIST

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