CLINICAL REVIEW

Application Type	sBLA
Submission Number	125276/22
Submission Code	P
Letter Date	October 14, 2010
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Reviewer Name	Kathleen M. Coyle, M.D.
Review Completion Date	March 22, 2011
Established Name	tocilizumab
(Proposed) Trade Name	Actemra
Therapeutic Class	Interleukin-6 Inhibitor
Applicant	Roche
Priority Designation	P
Formulation	Intravenous
Dosing Regimen	12 mg/kg for patients <30 kg and 8 mg/kg for patients ≥ 30 kg given once every 2 weeks
Indication	Systemic Juvenile Idiopathic Arthritis (sJIA)
Intended Population	sJIA patients ≥ 2 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend approval of this BLA with revisions to the proposed label.

1.2 Risk Benefit Assessment

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin 6 receptor (IL-6R). By preventing the binding of IL-6 to its receptor, TCZ inhibits the biological activity of IL-6. TCZ was approved by FDA under BLA 125276 on January 8, 2010. Currently it is approved (4 mg/kg with an increase to 8 mg/kg based upon clinical response) for the 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. Outside the US it was first approved in Japan on April 11, 2005 for the improvement of symptoms in patients with Castleman's disease. TCZ is currently approved in 95 countries for the treatment of adult onset moderate to severe RA. In India and Japan TCZ is also indicated for treatment in Castleman's disease, pJIA and sJIA.

Summary of Clinical Findings

Brief Overview of Clinical Program

The current sBLA 125276_22 is intended to provide data in support of the use of Actemra® at the doses of 12 mg/kg for patients < 30 kg and 8 mg/kg for patients > 30 kg 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. If approved, TCZ would be the first product specifically approved for the treatment of sJIA in the US.

Pivotal data for this application is from study WA18221, a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of TCZ in 112 patients with active sJIA, with a 92-week single arm open-label extension followed by a 3 year open label continuation of the study to examine the long term use of TCZ. This study (conducted under IND 11972) is subject to a SPA agreement (initial agreement on December 5, 2007 with an amendment on July 30, 2009). The application includes 12-week efficacy and safety data from WA18221-Part 1 (TCZ 12 mg/kg dose for patients with body weight <30 kg and 8 mg/kg dose for patients with body weight ≥30 kg) A cut of WA18221-Part 2 data is also included in the application (cut-off date: May 10, 2010) when 50 patients reached one year in Part II of WA18221; 3) additional supportive safety and efficacy data from Japanese sJIA trials containing data for at least 56 patients through to one year.

Further support for this application is provided by data from the Japanese Clinical Development program on sJIA conducted by Chugai Pharmaceutical Co Ltd. containing data for at least 56 patients through to one year. Actemra is approved in Japan (and India) for treatment of sJIA based upon these studies. The Chugai clinical program consists of 5 clinical studies. One study, an open label, single ascending dose study enrolling 18 patients was performed in Europe. The other 4 studies were conducted in Japan and enrolled a total of 149 sJIA patients aged 2 to 34 who received at least one dose of TCZ and have a total exposure of 326.3 patient years in the Chugai Japanese program.

Summary of Efficacy

The pivotal study, WA18221, and the two supportive long-term studies by Chugai (MRA317JP and MRA324JP) demonstrate a higher proportion of patients treated with TCZ achieved JIA ACR30/50/70/90 responses over time. At the same time the proportion of patients reducing the use of concomitant oral corticosteroids has also increased over time while on TCZ treatment, without loss of efficacy. Improvements in markers of disease activity (fever, CRP, ESR, thrombocytosis, leukocytes, SAA, and anemia) also demonstrated improvement toward normal levels with both short- and longer-term treatment with TCZ. Patients missing one or more doses of TCZ still maintained JIA ACR30/50/70/90 response rates and corticosteroid dose tapering over time.

Summary of Safety

Based on the known safety profile of TCZ in RA patients, in addition to previously identified risks of TCZ in sJIA patients (based on sJIA Chugai studies), primary AEs of interest included infections, macrophage activation syndrome (MAS), neutropenia, liver function test abnormalities, anaphylaxis and gastrointestinal perforation.

A higher overall AE rate was observed in sJIA patients than in RA patients The SAE rate was also higher in sJIA patients than in RA patients. In both sJIA and RA patients, the death rate was < 1.0 per 100 patient-years. The rate of premature treatment withdrawal for AE was lower in sJIA than in RA. The incidence of study drug dose modifications was similar in the two patient populations.

Infection AEs were the most frequent AEs in both sJIA and RA patient populations but were higher in sJIA patients than in RA patients (104 per 100 patient-years). The infection SAE rate was also higher in sJIA than in RA. In both pediatric patients with sJIA (based on study WA18221) and adult RA, < 1% of each patient population met the criteria of anaphylaxis according to the Sampson's analysis.

The incidence of MAS observed in WA18221, Chugai sJIA studies, and Chugai postmarketing surveillance (JPMS) studies was 2.7%, 2.7%, and 3.8%, respectively. These calculations compared favorably with the estimated background incidence of MAS between 6.8% and 8.2% in sJIA patients.

In WA18221, 13% and 2% of patients experienced CTC grade 3 and grade 4 neutropenia, respectively. 11% and <1% of patients experienced CTC grade 3 and grade 4 neutropenia, respectively, in Chugai sJIA studies. Compared with sJIA patients, CTC grade 3and grade 4 neutropenia (< 1%) occurred less frequently in RA patients.

Grade 3 and 4 elevations in ALT/AST values were observed more often in sJIA treated with TCZ: grade 3 ALT: 7% in study WA18221 and 7% in Chugai studies; grade 3 AST: 0.9% in study WA18221 and 4% in Chugai studies; grade 4 ALT: none in study WA18221 and 2% in Chugai studies; grade 4 AST: 0.9% in study WA18221 and 1% in Chugai studies) in RA patients (grade 3 ALT: 3%, grade 3 AST: < 1%, grade 4 ALT/AST: 1%).

In both pediatric patients with sJIA (based on study WA18221) and adult RA, < 1% of each patient population met the criteria of anaphylaxis according to the Sampson's analysis.

No GI perforations were reported in study WA18221. One GI perforation was reported in the Chugai supportive studies (study MRA011JP), duodenal perforation was observed in one patient, a 10 year old male with sJIA.

Risk-Benefit Assessment

The sJIA indication qualifies as an unmet medical need. TCZ treatment of sJIA in pivotal study WA18221, in addition to supportive sJIA Chugai studies, has demonstrated substantial and significant benefit compared to placebo. The safety profile of TCZ in sJIA when compared to that in RA does reveal an increased rate of SAE and AE. However, the background incidence of MAS is lower in TCZ-treated patients compared to historical cohorts. No new safety signals for TCZ have been demonstrated in the sJIA population compared to the RA population. Therefore, as demonstrated in controlled clinical trials, the benefits of TCZ treatment in sJIA far outweigh potential treatment risks.

1.3 Recommendations for Postmarketing Risk Management Activities

A Risk Evaluation and Mitigation Strategy (REMS) was recommended in the initial approval of TCZ for the RA indication. This included:

1) Monitoring and dose modification recommendations for absolute neutrophil count,
platelet count and liver enzymes.
Monitoring at 4-8 week intervals, with modification or interruption of TCZ dosing
as per instructions to be specified in labeling.
2) MedGuide

To assure communication to patients of the risks of tocilizumab treatment,
including serious infections, GI perforations, and necessity of laboratory monitoring.

Other than incorporation of the sJIA indication into the MedGuide, no additional postmarketing risk management activities are warranted.

1.4 Recommendations for other Post Marketing Study Commitments

No further post marketing study commitments are required for TCZ.

2 Introduction and Regulatory Background

2.1 Product Information

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin 6 receptor (IL-6R). By preventing the binding of IL-6 to its receptor, TCZ inhibits the biological activity of IL-6. TCZ was approved by FDA under BLA 125276 on January 8, 2010. Currently it is approved (4 mg/kg with an increase to 8 mg/kg based upon clinical response) for the 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. Outside the US it was first approved in Japan on April 11, 2005 for the improvement of symptoms in patients with Castleman's disease. TCZ is currently approved in 95 countries for the treatment of adult onset moderate to severe RA. In India and Japan TCZ is also indicated for treatment in Castleman's disease, pJIA and sJIA.

The current sBLA 125276_22 is intended to provide data in support of the use of Actemra® at the doses of 12 mg/kg for patients < 30 kg and 8 mg/kg for patients ≥ 30 kg 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. If approved, TCZ would be the first product specifically approved for the treatment of sJIA in the US. Pivotal data for this application is from study WA18221, a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of TCZ in 112 patients with active sJIA, with a 92-week single arm open-label extension followed by a 3 year open label continuation of the study to examine the long term use of TCZ. This study (conducted under IND 11972) is subject to a SPA agreement (initial agreement on December 5, 2007 with an amendment on July 30, 2009). The application includes 12-week efficacy and safety data from WA18221-Part 1 (TCZ 12 mg/kg dose for patients with body weight <30 kg and 8 mg/kg dose for patients with body weight ≥30 kg) A cut of WA18221-Part 2 data is also included in the application (cut-off date: May 10, 2010) when 50 patients reached one year in Part II of WA18221; 3) additional supportive safety and efficacy data from Japanese sJIA trials containing data for at least 56 patients through to one year.

Further support for this application is provided by data from the Japanese Clinical Development program on sJIA conducted by Chugai Pharmaceutical Co Ltd. containing data for at least 56 patients through to one year. Actemra is approved in Japan (and India) for treatment of sJIA based upon these studies. The Chugai clinical program consists of 5 clinical studies. One study, an open label, single ascending dose study enrolling 18 patients was performed in Europe. The other 4 studies were conducted in Japan and enrolled a total of 149 sJIA patients aged 2 to 34 who received at least one dose of TCZ and have a total exposure of 326.3 patient years in the Chugai Japanese program.

2.2 Currently Available Treatments for Proposed Indications

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 percent of all cases of JIA. Secondary complications (e.g. growth failure, osteoporosis, deformities and loss of function) and amyloidosis are the medical sequelae, with accompanying adverse developmental and social consequences.

Current therapy for sJIA include NSAIDs, methotrexate, systemic glucocorticoids, intravenous gamma globulin therapy, cyclosporine, thalidomide, anti-TNF therapy, and interleukin-1 inhibitors, yet none of these products have been approved for treatment of sJIA. Despite the use of currently available therapies, up to 50% of patients will have ongoing active arthritis and up to 30% will continue to experience systemic features of the disease 10-15 years after disease onset.

The Applicant requested priority review, as per the MAPP 6020.3 Review Classification Policy, due to the potential of TCZ to provide safe and effective treatment for sJIA where no satisfactory alternative therapy exists. The request for priority review was granted by the Agency for this application.

2.3 Availability of Proposed Active Ingredient in the United States

TCZ was approved by FDA under BLA 125276 on January 8, 2010 for the 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.

2.4 Important Safety Issues With Consideration to Related Drugs

TCZ is the only currently approved anti-IL6 therapy. From clinical studies conducted for the RA indication, the most common adverse reactions (incidence $\geq$ 5%) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT. Serious infections leading to hospitalization or death including tuberculosis, bacterial, invasive fungal, viral and other opportunistic infections have occurred in patients receiving TCZ. Other serious adverse events occurring with use of TCZ are gastrointestinal perforation, anaphylaxis or serious hypersensitivity reactions. Laboratory monitoring is recommended during TCZ therapy due to

potential consequences of treatment-related changes in neutrophils, platelets and liver function tests.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A brief summary of pre-submission regulatory activity related to the submission is as follows:

- September 21, 2004: pre-IND meeting held regarding a proposed phase III study based on open studies. The Agency recommended that the Sponsor delay phase III sJIA studies until the adult RA safety database was available
- March 20, 2007: EOP2 meeting held focusing on proposed clinical studies for both sJIA and pcJIA. For sJIA, WA18221 design, 1 and 2 endpoints, dose and sample size were agreed upon. An agreement was reached to file was made after Part I of WA18221 Part I was completed and after 50 patients had 1 yr data from WA18221 Part II. It was also agreed that added long term-data from Chugai's sJIA studies would be submitted (N=56).
- (b) (4)
- November 6, 2007 and December 5, 2007: SPA request (b) (4) was submitted and resulted in SPA agreement.
- June 16 2009 and July 30, 2009: Confirmation requested and received that the SPA remained in effect with an amendment to WA18221.
- May 10, 2010: pre-sBLA meeting held. The Agency agreed that proposed safety and efficacy data appeared adequate to support the application for sJIA indication. In addition, the Agency recommended exploration of the relationship between exposure/immunogenicity and efficacy/safety; comparison of pediatric safety data to overall safety; re-definition of anaphylactic reactions; and consistent definition of macrophage activation syndrome (MAS).

2.6 Other Relevant Background Information

All relevant background information is presented in Sections 2.1 to 2.6 above.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was complete, well-organized, and uncomplicated in hyperlinking references as necessary.

A DSI consult was not deemed necessary by the Agency. Although sJIA is an orphan indication, there is a scarcity of patients at any United States study sites. Thus, disqualification of any given site would be unlikely to affect overall study findings.

3.2 Compliance with Good Clinical Practices

The Applicant certified that submitted clinical study was conducted in compliance with good clinical practice guidelines. Quality control procedures to insure that the study was conducted, and that the data were generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory documents.

3.3 Financial Disclosures

The Applicant has adequately disclosed financial arrangements with the main clinical investigator and sub-investigators as recommended in the FDA guidance for industry and no potential conflicts of interest were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This sBLA does not include information in Module 3 of the eCTD submission. No additional CMC information is included in this submission since data collected during study WA18221 are directly applicable to the current commercially available material.

4.2 Clinical Microbiology

This sBLA contains no new clinical microbiology information.

4.3 Preclinical Pharmacology/Toxicology

A full review of preclinical pharmacology/toxicology aspects of this sBLA was conducted by Asoke Mukherjee, PhD. The reader is referred to Dr. Mukherjee's formal review for comprehensive details.

No additional non-clinical pharmacology investigations were performed to support
the use of TCZ in the pediatric indication of sJIA. To support clinical efficacy data, the application refers to published evidence for efficacy of inhibition of IL-6 signaling in
juvenile animal models.

As expected from the pleiotrophic nature of IL-6, the pathogenic role of IL-6 on bone matrix resorption, represents the systemic manifestation of chronic

inflammation associated with severe systemic skeletal side effects in these juvenile patients (Kwan Tat S et al., 2004; Dai J et al., 2000). Over-expression of IL-6 in pre-pubertal mice induces a skeletal phenotype closely resembling the systemic growth retardations as well as abnormalities of the skeletal muscle metabolism found in children with chronic inflammatory diseases (De Benedetti F et al., 2006; De Benedetti F et al., 2002). Inhibition of IL-6 was able to correct the skeletal pathology as well as the systemic muscles atrophy in these animal models (De Benedetti F et al., 2001).

In vitro, it has been shown that IL-6 inhibits the differentiation of osteoclast precursor cells into osteoclasts. However, in cocultures in vitro and in vivo, ICAM-1 released from synovial cells reversed IL-6-induced suppression of osteoclastogenesis (Suzuki M, 2010). Tocilizumab reduced RANKL expression and the number of osteoclasts in affected joints of monkeys with
collagen-induced arthritis (Kato A, 2008). These lines of evidence suggest that IL-6 augments osteoclast formation in vitro under appropriate tissue context conditions and in vivo.

A full set of animal toxicological studies is available for TCZ; this data was been presented and reviewed in the initial Nonclinical Overview (November 2007). The current sBLA presents additional information elaborated in the context of a toxicity study in juvenile mice with the rat IgG surrogate antibody to tocilizumab, MR16-1. A set of reproductive and pre/postnatal development studies was conducted earlier as well and was submitted in the supplementary documentation in 2009.

The sBLA submission includes a report of the study 'A Toxicity Study to Evaluate the Effects of MR16-1 on Postnatal Development and Growth in Juvenile Mice.' As studies with juvenile monkeys are limited in group size and require a long treatment duration of several years to cover all juvenile development stages from weaning until sexual maturation, a juvenile toxicity study was conducted in the mouse using a surrogate antibody for TCZ, MR16-1. Pharmacokinetic investigations submitted earlier imply that this study with MR16-1 was conducted under full inhibition of the IL-6R signaling cascade. Earlier studies yielded also evidence that MR16-1 is a useful surrogate antibody for TCZ for studies in the mouse (submitted with the BLA in 2007 and in reproductive toxicity studies submitted in 2009). The duration of the juvenile toxicity study starting at weaning and ending at onset of sexual maturity is intended to bridge the toxicology study program for TCZ. The program was conducted mainly in adult monkeys and studies

with its rodent surrogate MR16-1 were conducted during pregnancy and after birth in the lactation period. Apart from assessment of all general parameters of a toxicity study, the juvenile toxicity study focused specifically on post-weaning development and growth, immune system (including immunization response), skeletal development and sexual maturation as part of organ systems that may be impacted by inhibition of IL-6R signaling. The data from this study indicate that MR16-1 did not induce any meaningful changes on postnatal development and growth, skeletal development, and sexual maturation in juvenile animals. In addition, changes in lymphocyte subsets observed under treatment with MR16-1 did not impact on functional measurements of immune response. Thus, this study supports the safe use of TCZ in children and adolescents from birth until the fully adult age. Regarding the age of the animals investigated, this juvenile toxicity study is intended to bridge between a pre/postnatal development study with MR16-1 and toxicity studies in adolescent and adult monkeys with TCZ.

4.4 Clinical Pharmacology

A full review of clinical pharmacology aspects of this sBLA was conducted by Partha Roy, PhD. The reader is referred to Dr. Roy's formal review for comprehensive details.

The clinical pharmacology program included PK and PD data and PK-PD relationships from the following studies: Roche's pivotal study WA18221 and five supportive Chugai studies (LRO320, MRA011JP, MRA316JP, MRA317JP, and MRA324JP). In addition, two population PK analyses were also submitted: 1) development of alternative dosing regimen recommendations for pediatric patients with sJIA and low body weight and 2) verification of the alternative dosing regimen recommendation using data from study WA18221.

4.4.1 Mechanism of Action

IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis. IL-6 has been implicated in the pathogenesis of diseases including other inflammatory diseases, osteoporosis and neoplasia.

Tocilizumab selectively binds to soluble and membrane-bound human IL-6R, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6 The data obtained from *in vitro* assays demonstrate that tocilizumab has essentially no or minimal

complement dependent cytotoxicity (CDC) activity, and little or no significant antibody dependent cellular cytotoxicity (ADCC) activity.

4.4.2 Pharmacodynamics

Inflammatory pharmacodynamic markers such as C-reactive protein (CRP), Eryththrocyte sedimentation rate (ESR), Acute phase serum amyloid A (SAA) were monitored in study WA18221 while IL-6 and sIL-6R, directly linked to the mechanism of action of TCZ, were also measured. Following administration of TCZ, a rapid decline in mean CRP, ESR, and SAA was observed in the two dose groups (8 mg/kg and 12 mg/kg) with significant decreases seen by Week 2 and remaining suppressed through 12 weeks of treatment.

Following TCZ administration, IL-6 levels initially increased rapidly and then generally decreased with time, although mean concentrations did not reach baseline levels by Week 12 in either dose group. Mean sIL-6R increased rapidly by Week 2 and continued to increase toward a plateau. The observed changes in IL-6 and sIL-6R were similar between dose groups. These changes were not observed in patients receiving placebo.

The changes of inflammatory markers (CRP, ESR, and SAA) and markers of the TCZ mechanism of action (IL-6 and sIL-6R) were similar between two dose groups providing support for the proposed BW based dosing regimen in this pediatric patient population. In addition, there was no appreciable relationship between TCZ trough concentrations and PD markers tested as PD responses are generally complete at the range of steady-state clinical concentrations of TCZ in both dose groups.

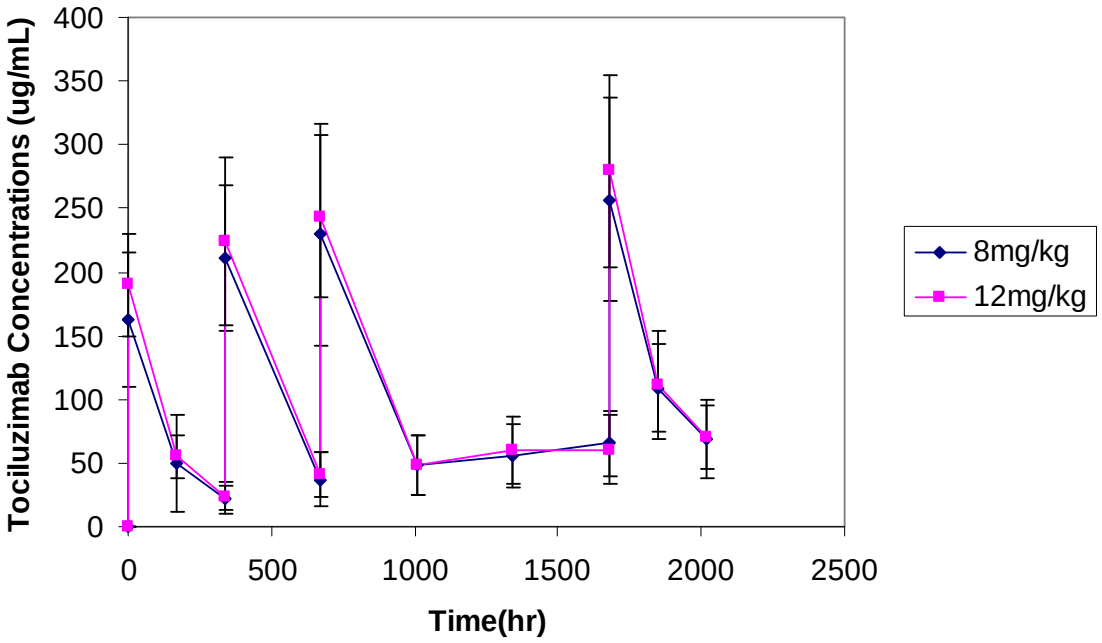
4.4.3 Pharmacokinetics

The dosing regimen is primarily selected based on pharmacokinetic analysis of data from sJIA patients in study MRA316JP. After 6 weeks of treatment with TCZ 8 mg/kg every 2 weeks, the proportion of patients who reached the ACR50 response was lower in patients < 30 kg (83%) than in patients weighing ≥ 30 kg (100%). Similarly, the proportion of patients who reached ACR70 was also lower in patients < 30 kg (63%) than those ≥ 30 kg (85%). This difference was explained by the visible trend toward lower systemic exposure to TCZ in patients with lower BW.

A population PK modeling and simulation was thus performed using pooled PK data from Chugai studies MRA316JP and LRO320 to explore an alternative dosing regimen achieving uniform exposure across the entire BW range. The post-hoc estimates of systemic exposures of TCZ using final population PK model predicted that the 12 mg/kg dose in patients < 30 kg would yield similar systemic TCZ exposure as patients ≥ 30 kg. TCZ 8 mg/kg (patients ≥ 30 kg) and 12 mg/kg (patients < 30 kg) every two weeks was evaluated in pivotal study WA18221. This dosing regimen resulted in similar serum concentrations at sampling time points over time (Figure 1) and similar systemic exposure (Table 1) between the BW categories (< 30 kg and ≥ 30

kg). Additionally, 94.7% and 75.5% of patients achieved the primary efficacy endpoint of JIA ACR30 response and absence of fever at Week 12 (ITT population) for 12 mg/kg (<30 kg bodyweight) and 8 mg/kg (≥ 30 kg bodyweight) dosing, respectively compared to only 24.3% in the placebo group.

Figure 1. Tocilizumab serum concentrations (Mean ± SD) in sJIA patients with BW <30 kg (12 mg/kg) and ≥30 kg (8 mg/kg) in study WA18221.



Source: Figure 1, Dr. Roy's Clinical Pharmacology review.

Table 1. Summary of model-predicted TCZ PK measures at week 12 by dosing groups

Parameter		8 mg/kg n = 37	12 mg/kg n = 38	All patients N= 75
C_{max}, µg/mL	Mean ±SD	226 ±54.5	263 ±54.1	245 ±57.2
	CV%	24.1	20.6	23.3
C_{min}, µg/mL	Mean ±SD	54.5 ±20.7	60.5 ±25.5	57.5 ±23.3
	CV%	38.0	42.1	40.5
$AUC_{2\ weeks}$, µg·Day/mL	Mean ±SD	1337 ±409	1346 ±426	1341 ±415
	CV%	30.5	31.6	30.9

Source: Table 1, Dr. Roy's Clinical Pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 2. Tocilizumab Clinical Studies in sJIA

Tocliizumab: Clinical Studies in sJIA						
Study Number Phase	**Number of Study Centers Locations**	**Study Design**	**Treatment Dose/Regimen**	**Gender M/F**	**Duration**	**Number Patients/ Disposition/ Age Range**
PIVOTAL STUDY WA18221 Phase III	43 centers 17 countries	5 yr, 3-part study Pt I: 12 Wk, R, DB, PC Pt II: 92 Wk, single arm OL extension Pt III: 3 Yr, OL continuation	Grp I: TCZ q 2wk (8 mg/kg for >/= 30 kg; 12 mg/kg pts <30 kg) Grp II: PBO q 2 wk with escape option	56 M 56 F	Pt I: 12 wk Pt II: 92 wk Pt III: 3 yr	112 dosed 3 w/drawn Part I 20 escaped to TCZ 109 completed Pt I 9 w/drawn Pt II (as of 10-May-10 Age 2-17 yrs
LRO320 Phase II	3 EU sites 2 UK 1 France	Multi-center OL, single dose cohort dose escalation	TCZ 2, 4 or 8 mg/kg 6 pts per cohort (3 per age group 2 age groups per dose level (1-5 yrs and 6-18 yrs)	10 M 8 F	Single dose	18 dosed 0 withdrawn 18 completed Age 2-17 yrs
MRA011JP Phase II	Dept Pediatrics Yokohama City University Hospital	Single-center, OL, intra-pt dose escalation/ titration study with extension phase	TCZ 2 mg/kg q 2 wks x 3, 16(42%) CRP response; 4 or 8 mg/kg q 2 wks	8 M 3 F	6-14 wks (dose escalation) then > 1 yr extension phase	11 dosed 1 w/drawn (extension) 10 completed Age 3-18 yrs
MRA316JP Phase III	8 sites in Japan	Multi-center, DB, R, PC withdrawal study	TCZ 8 mg/kg q 2 wk x 3 (open phase) then 8 mg/kg or PBO q 2 wks x 6 (DB withdrawal phase)	21 M 35 F	6 wks followed by 12 wk withdrawal phase	Open Label: 56 dosed 6 withdrawn 50 completed Age 2-19 yrs Blind Phase: 21 TCZ; 23 PBO 3 w/drawn; 41 completed
MRA317JP Phase III (Long-Term Extension)	8 sites in Japan	Multi-center OL extension for MRA011JP and MRA316JP	31(82%)	29 M 38 F	study continued until commercially available ~ 5 yrs	67 dosed (11 from MRA011JP and 56 from MRA316JP) 2 withdrawn 58 completed
MRA324JP Phase III (Expanded Access Program)	13 sites in Japan	Multi-center OL expanded access study (refractory sJIA patients)	TCZ 8 mg/kg q 2 wk dosing interval can be shortened to 1 week	39 M 42 F	study continued until commercially available ~ 5 yrs	82 dosed (81 in FAS)* Age 2-34 yrs; including 11 pts >/= 20 yrs old 8 withdrawn 74 completed

*Study MRA324JP had 82 patients, but one patient was excluded from the study due to presence of Takayasu's disease, thus reducing the FAS to 81 patients.
R, randomized; DB, double-blind; PC, placebo-controlled; OL, open-label
Source: Summary of Clinical Efficacy, Table 1.

The U.S. supplemental biologics license application (sBLA) is comprised of one controlled pivotal study and five supportive clinical studies as shown in Table 2 above.

5.2 Review Strategy

With regard to efficacy, pivotal study WA18221 was reviewed individually for the primary endpoint of ACR20 response and absence of fever at Week 12 and key secondary endpoints, such as ACR50/70/90 responses at Week 12. Supportive data from Phase III Chugai sJIA studies were also reviewed with particular attention to the primary and key efficacy endpoints from each study. Safety analyses and data pooling is described in Section 7.1 below.

5.3 Discussion of Individual Studies

Study WA18221

Study WA18221, is a pivotal Phase III double-blind, placebo-controlled, parallel group multi-center, 2-arm study conducted in three parts to evaluate the efficacy and safety of TCZ in patients with active sJIA:

- Part I: the primary endpoint is a comparison between TCZ and placebo of the proportion of patients with a JIA ACR30 response with absence of fever at Week 12
- Part II: a 92-week, single-arm, open-label extension to examine the long-term use of TCZ on efficacy and safety
- Part III: a three-year single-arm, open-label continuation of the study

This study enrolled 112 subjects and was conducted internationally across 43 centers in 17 countries worldwide, including the US. The primary endpoint was the proportion of patients with a JIA ACR 30 response and absence of fever at 12 weeks.

Chugai Supportive Studies

Study LRO320

Study LRO320 was a Phase II open-label, single-ascending-dose study conducted in France and the UK to investigate the safety and pharmacokinetic (PK) aspect of TCZ in 18 children with sJIA. Two age groups, 2 to 5 (Group 1) and 6 to 18 years (Group 2), were administered a single dose at 2, 4, or 8 mg/kg with three patients per age and dose group. The study involved pediatric patients with sJIA who had an inadequate response to NSAIDs and to corticosteroids (prednisolone or equivalent ≥ 0.2 mg/kg/day). The primary objective was to determine the safety and tolerability of single, ascending doses of TCZ (2 mg/kg, 4 mg/kg, and 8 mg/kg) and the PK profile of a range of TCZ doses.

Study MRA011JP

Study MRA011JP was a Phase II, open-label study in pediatric patients with sJIA with inadequate response to corticosteroids (≥ 3 months at dose of ≥ 0.2 mg/kg as prednisolone

equivalent). This study was designed to evaluate time courses of CRP and ESR of TCZ doses (2 mg/kg, 4 mg/kg, and 8 mg/kg) three times at 2-week intervals in the 12-week main evaluation period and the long-term treatment for ≥ 1 year in the extended treatment period. Intra-patient bi-weekly dose escalation of TCZ from 2 mg/kg to 4 mg/kg to 8 mg/kg was allowed based on measurement of CRP.

This study was a forced dose titration study. Eleven patients with sJIA from 2 to 19 years of age started TCZ 2 mg/kg at the anticipated 2-week dosing intervals. In this study, CRP was used as an index of disease activity and the dose of TCZ was adjusted to the next higher dose if the CRP remained >15 mg/L 1-2 weeks after the first dose of TCZ at a given dose. Subsequent possible dose levels were 4 mg/kg and 8 mg/kg. The dose level without active inflammation (defined as CRP<15 mg/L) was administered 3 times in total, maintaining a 2-week dosing interval. Among the 11 patients treated, 3, 5, and 3 patients received a final dose of 2, 4, and 8 mg/kg respectively to maintain the CRP<15 mg/L.

Study MRA316JP

Study MRA316JP was a Phase III, dual-phase (open-label and blind period) study in pediatric patients with sJIA in Japan who failed to respond adequately to corticosteroid treatment for ≥3 months at a dose of ≥0.2 mg/kg prednisolone equivalent. This was a randomized withdrawal study designed to assess the efficacy, rate of maintained response, safety, and PK of TCZ administered to 56 children with sJIA at a dose of 8 mg/kg three times at 2-week intervals in both an open-label and subsequently a double-blind period where patients received either TCZ 8 mg/kg or placebo. In the open-label period, the primary endpoint was percentage of patients demonstrating a 30% improvement in the JIA ACR core set and improvement in CRP (< 5 mg/L) on the last observation day.

On the last observation day of the open-label period, patients with a CRP value of < 5 mg/L and at least a JIA ACR30 response were entered into the blind period. The primary endpoint in the blind period was the rate of maintained response, defined as patients not withdrawn from the study as a result of withdrawal criteria or becoming a subject of rescue two weeks after last observation (two weeks after the sixth infusion in blind period). Patients who lost their response (< JIA ACR30 or CRP ≥15 mg/L) during the blind period were designated as non-responders for the analysis and treated with open-label TCZ as rescue treatment and allowed to continue on to a subsequent long-term treatment study (MRA317JP).

Study MRA317JP

Study MRA317JP was a Phase III, open-label, long-term treatment study of pediatric patients who were enrolled in studies MRA011JP and MRA316JP and transitioned into this study for longer-term treatment assessments in efficacy, safety, and PK, from the first infusion of TCZ at 8 mg/kg from the previous study.

Sixty-seven patients, 11 from study MRA011JP and 56 from study MRA316JP were enrolled in MRA317JP. Patients received TCZ 8 mg/kg every 2 weeks until TCZ was commercially available. The dosing interval could be adjusted according to the disease activity at the discretion of the investigators. Long-term efficacy and safety data were analyzed for the combined data from the start of the main studies, i.e., MRA011JP and MRA316JP, to the end of this study (the MRA011JP/316JP/317JP population). In the MRA011JP/316JP/317JP population, 67 patients received at least one dose of TCZ.

Study MRA324JP

Study MRA324JP was a long-term, open-label study initiated to provide expanded access to TCZ for patients with sJIA in Japan who were showing resistance to existing treatments. This study provided patients with the opportunity to receive TCZ at 8 mg/kg and to investigate the safety, efficacy, and PK of TCZ when used long term. Inclusion/exclusion criteria were less stringent, e.g., there were no criteria for CRP compared to prior studies because it was anticipated that patients who would likely participate in this type of study would be dependent on high-dose corticosteroid and unlikely to show elevation in CRP or other inflammatory symptoms. The primary endpoint in this study was the evaluation of safety. Efficacy endpoints were included as secondary endpoints.

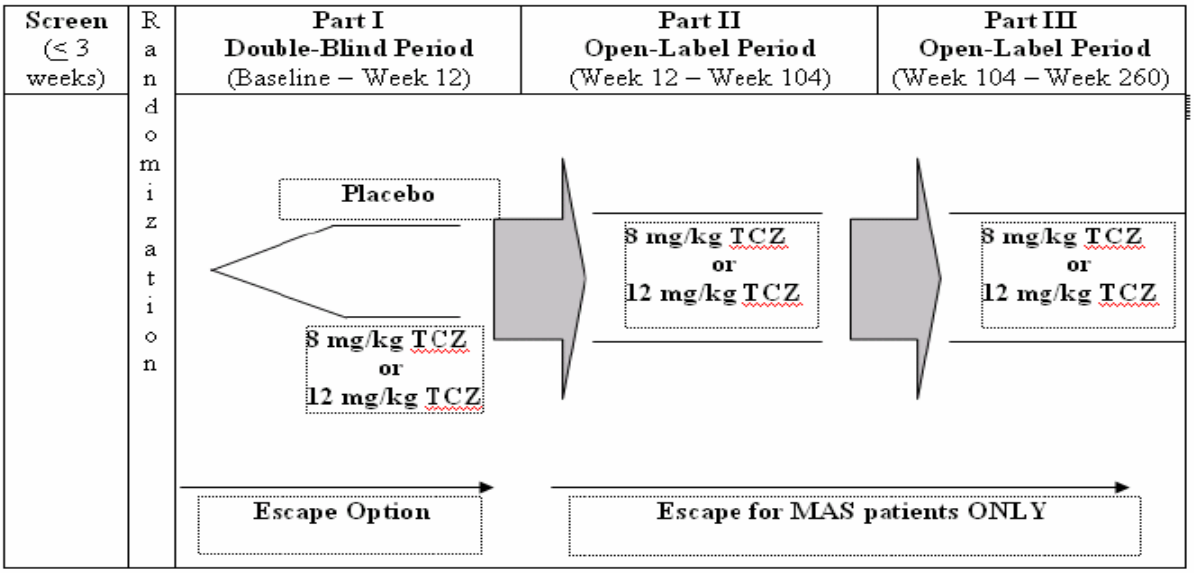
6 Review of Efficacy

Efficacy Summary

6.1 Indication

6.1.1 Methods

Figure 2. Study WA18221 Study Design



Source: Study WA18221 CSR, Figure 1.

The overall design of the study is depicted in Figure 1 above. Following screening, eligible patients were randomized into Part I of the study and received either TCZ or placebo by IV infusion in a 2:1 ratio respectively.

In the TCZ group, patients < 30 kgs received a dose of 12 mg/kg and patients ≥30 kgs received a dose of 8 mg/kg every two weeks for six doses. 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) (< 30 kgs to/from ≥30 kgs).

Patients could have their CSs tapered following the specific CS Guidelines (detailed in the clinical protocol) at Week 6 and/or Week 8 if they acquired a JIA 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 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.

6.1.2 Demographics

Table 3. WA18221 General Demographic Variables at Baseline

WA18221 Summary of General Demographic Variables at Baseline (ITT Population)				
	PBO N=37	TCZ 8 mg/kg N= 37	TCZ 12 mg/kg N= 38	ALL TCZ N=75
SEX				
Male	20(54%)	16(43%)	20(53%)	36(48%)
Female	17(46%	21(57%)	18(47%)	39(52%)
RACE				
American Indian/Alaska	2(5%)	0	0	0
Black	0	1(3%)	0	1(1%)
Other	3(8%)	1(3%)	6(16%)	7(9%)
White	32(86%)	35(95%)	32(84%)	67(89%)
AGE (YEARS)				
Mean (SD)	9(4%)	14(3%)	7(3%)	10(5%)
WEIGHT (KG)				
Mean (SD)	32(17%)	50(20%)	20(6%)	35(21%)
HEIGHT (CM)				
Mean (SD)	121(20%)	145(16%)	108(14%)	126(24%)
ETHNICITY				
Hispanic	12(32%)	7(19%)	13(34%)	20(27%)
Non-Hispanic	25(68%)	30(81%)	25(66%)	55(73%)
REGION				
Europe	18(49%)	25(68%)	18(47%)	43(57%)
North America	8(22%)	9(24%)	7(18%)	16(21%)
Rest of the World	1(3%)	2(5%)	2(5%)	4(5%)
South America	10(27%)	1(3%)	11(29%)	12(16%)

Source: Adapted from WA18221 Clinical Study Report, Table 7.

Table 4. WA18221 sJIA Core Components at Baseline

WA18221 sJIA ACR Core Components at Baseline (ITT Population)				
	PBO N=37	TCZ 8 mg/kg N= 37	TCZ 12 mg/kg N= 38	ALL TCZ N=75
No. of Active Joints (0-71)				
n	37	37	38	75
Mean	17	24	19	21
No. of Joints with Limitation of Movement (0- 67)				
n	37	37	38	75
Mean	18	23	18	21
Patient/Parent Global Assessment VAS (0-100 mm)				
n	37	37	38	75
Mean	56	61	59	60
Physician Global Assessment VAS (0-100 mm)				
n	37	37	38	75
Mean	61	68	71	70
CHAQ-DI Score (0-3)				
n	37	37	38	75
Mean	1.7	1.7	1.8	1.7
ESR (mm/hr)				
n	37	37	38	75
Mean	54	51	64	58

Source: Adapted from WA18221 Clinical Study Report, Table 7.

Table 5. WA18221 Summary of sJIA Disease Characteristics at Baseline

WA18221 Summary of sJIA Disease Characteristics at Baseline (ITT Population)				
	PBO N=37	TCZ 8 mg/kg N= 37	TCZ 12 mg/kg N= 38	ALL TCZ N=75
Fever Status (last 7 D)				
absent	17(46%)	25(68%)	18(47%)	42(57%)
present	20(54%)	12(32%)	20(52%)	32(43%)
Fever Status (last 14 D)				
absent	13(35%)	22(59%)	12932%)	24(45%)
present	24(65%)	15(41%)	26(68%)	41(55%)
Rash Status				
free	19(51%)	28(76%)	25)66%)	52(71%)
present	18(49%)	8(22%)	12(34%)	21(28%)
No previous DMARDS				
Mean	1.4	1.6	1	1.2
SD	1.4	1.2	0.9	1.1
No previous DMARDS Category				
0	12(32%)	9(32%)	8(22%)	12(32%)
1	11(20%)	11(30%)	18(47%)	29(39%)
2	9(24%	8(22%)	5(13%)	13(17%)
>=3	5(14%)	10(27%)	3(8%)	13(17%)
No previous Biologics				
Mean	1.6	2.5	1.4	1.9
SD	1.3	1.5	1.1	1.4
No previous Biologics Category				
0	8(22%)	2(5%)	10(26%)	12(16%)
1	12(32%)	10(27%)	9(24%)	19(25%)
2	8(22%)	7(19%)	14(37%)	21(28%)
>=3	9(24%)	18(49%)	5(13%)	23(31%)
CRP (mg/L)				
Mean	96	232	169	200
SD	69	525	269	420
JADI-A (Articular Damage (0-72)				
Mean	5	5.2	5	5.1
SD	5.6	7.6	8.3	8
JADIE (Extraarticular Damage (0-17)				
Mean	1.7	1.4	1.4	1.4
SD	1.7	1.8	2	1.9
Tanner Stage (1-5)				
Mean	1.5	3	1.1	2
SD	1.5	3	1.1	2

Source: Adapted from WA18221 Clinical Study Report, Table 8.

Table 3, Table 4, and Table 5 above depict the baseline demographic variables, ACR sJIA core components, and sJIA disease characteristics of the subjects in study WA18221. Subjects were predominantly white, non-Hispanic from European study sites. There was an equivalent distribution of males and females. Mean age was lower in the 12 mg/kg group compared to PBO and the TCZ 8 mg/kg group. The lower mean age of the TCZ 12 mg/kg group (7 +/-3 years) versus the TCZ 8 mg/kg group (14 +/- 3 years) is reflective of the 12 mg/kg dose being administered to subjects < 30 kg. Mean sJIA core components at baseline were comparable across groups. Overall sJIA disease characteristics were similar, although placebo group mean CRP (96 +/- 69 mg/L) was lower than the TCZ 8 mg/kg (CRP 232 +/-525 mg/L) and TCZ 12 mg/kg (CRP 169 +/- 269 mg/L) groups. Differences in Tanner stage between the TCZ 8 mg/kg (3 +/- 3) and TCZ 12 mg/kg (1.1 +/- 1.1) groups are most likely reflective of the 12 mg/kg dose being administered to subjects < 30 kg.

Table 6. Summary of Stratification Variables at Baseline (WA18221 ITT Population)

WA18221 Summary of Stratification Variables at Baseline by Trial Treatment (ITT Population)				
	PBO N=37	**TCZ 8 mg/kg N= 37**	**TCZ 12 mg/kg N= 38**	**ALL TCZ N=75**
Weight (kg)				
< 30 kg)	21(57%)	0	38(100%)	38(51%)
>/= 30 kg	16(43%)	37(100%)	0	37(49%)
Duration sJIA Disease (years)				
Mean	5	6	4	5
SD	4.5	4.4	3.1	4
Duration sJIA Disease Category				
<4 years	19(51%)	16(43%)	22(58%)	38(51%)
>4 years	18(49%)	21(57%)	16(42%)	37(49%)
Background oral CS dose (mg/kg)				
Mean	0.27	0.21	0.36	0.29
SD	0.17	0.15	0.17	0.18
Background oral CS dose Category				
<0.3 mg/kg/day	19(51%)	28(76%)	10(26%)	38(51%)
>/= 0.3 mg/kg/day	18(49%)	9(24%)	28(74%)	37(49%)
Background MTX dose				
NO	11(30%)	16(43%)	7(18%)	23(31%)
YES	26(70%)	21(57%)	31(82%)	52(69%)

Prednisolone equivalent was used in calculation of oral corticosteroid (CS) dose
Source: Adapted from Summary of Clinical Safety, stdm11_stra_itt, page51

The above Table 6 summarizes stratification variables at baseline by trial treatment. Notable differences between groups are the TCZ 12 mg/kg group higher background oral CS (0.36 +/- 0.17); oral CS dose category (74% on >0.3 mg/kg/day) and MTX (82% use) compared to both PBO (0.27 +/- 0.17; 49% on > 0.3 mg/kg/day; 70% MTX use) and TCZ 8 mg/kg groups (0.21 =/- 0.18; 24% on > 0.3 mg/kg/day; 57% MTX use). sJIA disease duration was approximately equal across groups, but a greater proportion of patients had disease duration > 4 years in the TCZ 8 mg/kg group (57%) compared to the PBO (49%) and TCZ 12 mg/kg groups.

Table 7. Chugai sJIA Studies Demographics and Baseline Disease Characteristics

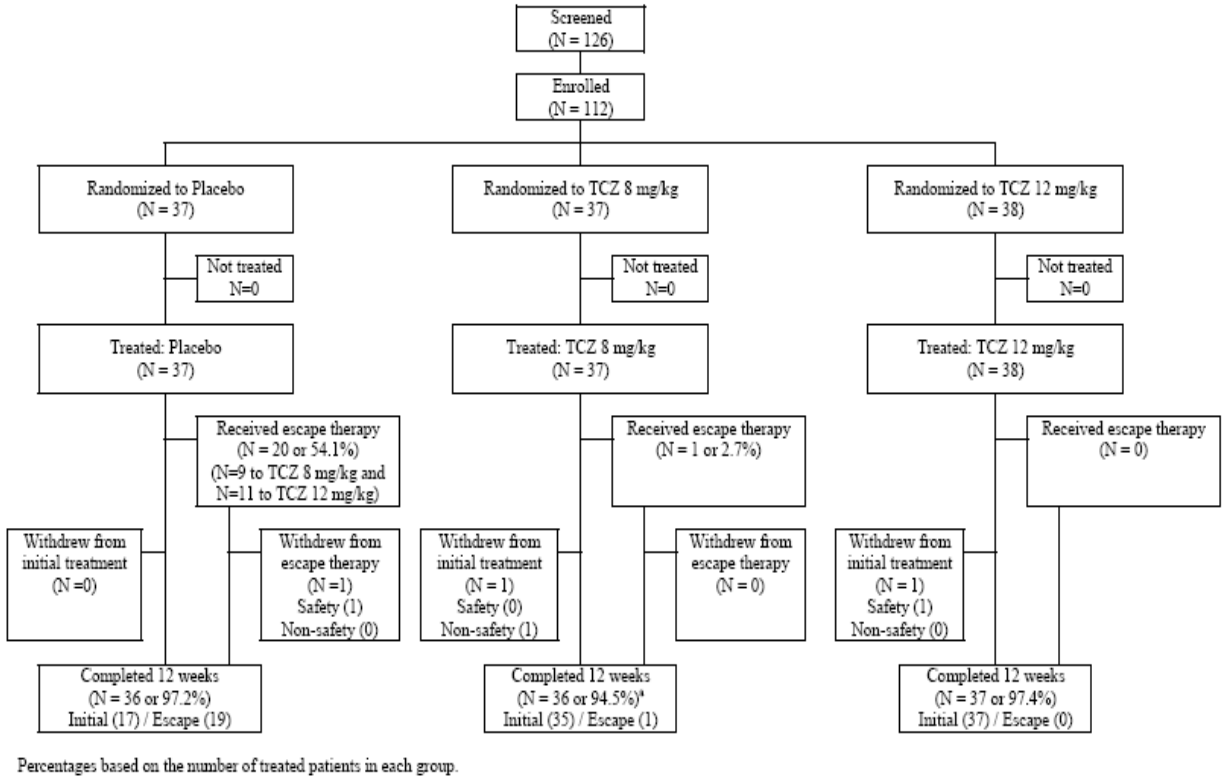
Demographic and Baseline Disease Characteristics in Chugai sJIA Studies			
	MRA011JP/316JP/317JP N=67	MRA324JP N=82	Total N=149
Gender			
Male	29(43)	39(48)	68(46)
Female	38(57)	43(52)	81(54)
Age (yrs)			
Mean +/- SD	8 +/- 4	11 +/- 7	10 +/- 6
<7 yrs old	25(37)	24(29)	49(33)
7-15 yrs old	36(54)	39(48)	75(50)
15-20 yrs old	6(9)	8(10)	14(9)
≥20 yrs old	0	11(13)	11(7)
Body Weight (kg)			
Mean +/- SD	28 +/-12	8 +/- 4	31 +/- 13
<30 kg	42(63)	38(46)	80(54)
30-50 kg	23(34)	33(40)	56(38)
≥50 kg	2(3)	11(13)	13(9)
Disease Duration (yrs)			
Mean +/- SD	4 +/- 4	6 +/- 6	6 +/- 5
No. prior DMARDS			
Mean +/- SD	2 +/-1	3 +/- 2	2 +/- 2
Corticosteroid dose			
(PSL eq. mg/kg)	0.5 +/- 0.4	0.7 +/- 0.5	0.6 +/- 0.4
No. active joints			
Mean +/- SD	7 +/-8	2 +/- 6	4 +/- 7
CRP (mg/dL)			
Mean +/- SD	6 +/-6	2 +/- 3	4 +/- 5

Source: Summary of Clinical Safety, Table 14.

The demographics and disease characteristics of subjects in the Chugai sJIA studies are described in Table 7 above. There was equal distribution of both sexes in the studies. Mean subject age in all studies was 10 +/- 6 years; mean disease duration ranged from 4 to 6 years. The presence of active disease is demonstrated by mean corticosteroid dose, number of active joints and CRP.

6.1.3 Patient Disposition

Figure 3. WA18221 Patient Disposition



Source: WA18221 CSR, Figure 1, p 103.

Figure 3 shows patient disposition in study WA18221 up to Week 12. Of the 37 treated PBO patients: 20 (54%) received escape therapy. 19 escape and 17 initial subjects completed 12 weeks (total 97%). 37 subjects were treated with TCZ 8 mg/kg; 1 withdrew from initial treatment and one received escape therapy. Overall, 94% completed 12 weeks. Of the 38 subjects treated with TCZ 12 mg/kg, one withdrew for safety reasons; 97% completed 12 weeks.

6.1.4 Analysis of Primary Endpoint(s)

Table 8 WA18221 Primary Endpoint

WA18221 Summary and Analysis of the Percentage of Patients with a JIA ACR30 Response and Absence of Fever at Week 12 (ITT Population)				
	PBO N=37	TCZ 8 mg/kg N= 37	TCZ 12 mg/kg N= 38	ALL TCZ N=75
N	37	37	38	75
Responders	9 (24%)	28 (76%)	36 (95%)	64 (85%)
95% CI	[10, 38]	[62, 90]	[88, 100]	[77, 93]

Source: Adapted from WA18221 Clinical Study Report Table 12.

The primary endpoint for study WA18221 was the proportion of patients with a JIA ACR30 response with absence of fever at Week 12. As shown in Table 8 above, the primary endpoint was achieved in 95% of the TCZ 12 mg/kg group, 76% of the TCZ 8 mg/kg group and 24% of PBO group. The percentage of responders was 85% in TCZ-treated patients versus 24% treated with PBO. This difference was significantly different at a p value < .0001. Because the study was not powered to detect differences between the TCZ 8 mg/kg and 12 mg/kg doses for any efficacy endpoint, statistical testing was not performed on the comparison between these two dose groups.

Table 9. Sensitivity Analysis: WA18221 Primary Endpoint

Summary and Analysis of the Percentage of Patients with a JIA ACR30 Response and Absence of Fever at Week 12-- All TCZ vs. Placebo (PP Population)		
	PBO (N=31)	ALL TCZ (N=64)
N	31	64
Responders 95% C.I.	9 (29%) [13; 45]	56 (88%) [79; 96]
Weighted difference vs. Placebo 95% C.I. of weighted difference		57 [39; 76]
p-value		<0.0001

Responders are patients who had a JIA ACR30 response at Week 12 and absence of fever (temperatures <37.5C) the Week 12 assessment day.
Patients who withdrew, received escape medication, or for whom the endpoint could not be determined are classified as non-responders.
LOCF rule applied to missing JIA ACR core set components at Week 12.
Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at Baseline.
Treatment comparison is vs. Placebo.
C.I. = Confidence Interval.

Source: Study WA18221 CSR Table 13.

The primary efficacy endpoint was repeated using the PP population, which consisted of patients in the ITT population who completed the study without major violation of entry criteria or protocol procedures. In the PP population, 56 TCZ patients and nine placebo patients met the primary endpoint (Table 9 above). Of those patients who were included in PP population, 88% of the TCZ patients and 29% of the PBO patients responded, a statistically

significant difference (p<0.0001).

6.1.5 Analysis of Secondary Endpoints(s)

Table 10. WA18221 Patients with JIA ACR30/50/70/90 Responses at Week 12.

Summary and Analysis of the Percentage of Patients with a JIA ACR3050/70/90 Responses at Week 12 (ITT Population)				
	PBO N=37	TCZ 8 mg/kg N= 37	TCZ 12 mg/kg N= 38	ALL TCZ N=75
JIA ACR 20 Response				
Responders	9(24%)	31(84%)	37(97%)	68(91%)
95%CI	[10, 38]	[72,95]	[92,100]	[84,97]
Weighted difference vs PBO				67
95% CI of Weighted Difference				[51,83]
p				**< .0001**
JIA ACR 50 Response				
Responders	4(11%)	29(78%)	35(92%)	64(85%)
95%CI	[0.8,21]	[65,92]	83,100]	[77,92]
Weighted difference vs PBO				74
95% CI of Weighted Difference				[58,90]
p				**< .0001**
JIA ACR 70 Response				
Responders	3(8%)	25(68%)	28(74%)	53(71%)
95%CI	[0,17]	53,82]	[60,88]	[60,81]
Weighted difference vs PBO				63
95% CI of Weighted Difference				[46,80]
p				**< .0001**
JIA ACR 90 Response				
Responders	2(5%)	13(25%)	15(40%)	28(37%)
95%CI	[0,13]	[20,51]	[24,55]	[26,48]
Weighted difference vs PBO				33
95% CI of Weighted Difference				[17,50]
p				**< .0001**

Source: Adapted from WA18221 CSR Table 16.

As shown in Table 10 above, the secondary endpoints of JIA ACR 20, 50, 70 and 90 responses were achieved in 91% (JIA ACR 20); 87% (JIA ACR 50), 71% (JIA ACR 70) and 37% (JIA ACR 90) of subjects. These responses were all significantly different from PBO at a p value <0.0001.

Table 11. Study WA18221 Summary of Secondary Endpoint Results

Study WA18221 Summary of Added Secondary Endpoint Results			
Secondary Endpoint	**ALL TCZ**	**PBO**	**p-value**
Proportions of patients with fever @ baseline fever free Wk 12	92%	73%	<0.0001
Proportions of patients with normalization of CRP @Wk 12	99%	6%	<0.0001
% change from baseline in ESR Wk 12	-88%	34%	<0.0001
% CFB CHAQ-DI Wk 12	77%	19%	<0.0001
% CFB PGA Disease Activity VAS @ Wk 12	-70%	-41%	0.0005
% CFB PGA Overall Well-Being VAS @ Wk 12	-66%	-1%	<0.0001
Proportion with baseline anemia: Hgb >10 g/L @ Wk 12	88%	3%	<0.0001
Proportion with baseline anemia: Hgb >10 g/L @ Wk 6	88%	3%	<0.0001
Proportion with rash @ baseline rash-free @ Wk 12	64%	11%	0.0008
CFB in pain VAS @ Wk 12	-41%	-1%	<0.0001
Proportion with MCD improvement in CHAQ-DI @ Wk 12	77%	19%	<0.0001
Proportion of ACR 70 reducing oral CS @ least 20% w/o subsequent flare or systemic symptoms to Wk 12	24%	3%	0.03
Proportion with baseline thrombocytosis normalized @ Wk 12	90%	4%	<0.0001
Proportion with baseline leukocytosis normalized @ Wk 12	75%	10%	<0.0001
Proportion with baseline anemia normalized Wk 12	80%	7%	<0.0001
% CFB number joints with active arthritis Wk 12	-71%	-37%	0.0012
% CFB number joints with limited movement Wk 12	-52%	-23%	0.0192

Source: Adapted from Summary of Clinical Efficacy, pages 58-62.

Table 11 above summarizes the remaining secondary endpoint results from study WA18221 (see Table 10 for JIA ACR secondary endpoint results). As seen in Table 11, with three exceptions, TCZ was significantly different from PBO in all secondary endpoints at a p value of <0.0001. The remaining secondary endpoints also evidenced significant differences in TCZ vs PBO: proportion of patients achieving JIA ACR 70 who reduced oral corticosteroids by at least 20% without subsequent flare or systemic symptoms to Week 12 (p= 0.03); % change from baseline of number of joints with active arthritis at Week 12 (p=0.001) and % change from baseline of the number of joints with limited movement at Week 12 (p= 0.02)

6.1.6 Other Endpoints

Several exploratory endpoints were analyzed. The results are summarized as follows:

Area under the curve for JIA ACR Core Components: No clear patterns observed with regard to treatment groups.

Serum Amyloid A: Thirty-two (86%) placebo patients and 62 (83%) TCZ patients had an abnormal SAA at Baseline. Of those patients, 57 (92%) TCZ patients and two (6%) PBO patients had their SAA return to normal range. This difference was statistically significant (p<0.0001).

Serum Ferritin: Twenty-three (31%) TCZ patients and 15 (41%) placebo patients had abnormal serum ferritin at Baseline. Of those patients, 21 (91%) TCZ patients and two (13%) PBO patients had their serum ferritin returned to the normal range. This difference was statistically significant (p<0.0001).

Insulin Resistance: The proportion of patients with a decrease in Homeostasis Model Assessment (HOMA) insulin resistance (fasting insulin [µU/ml] x fasting glucose [mmol/L]) / 22.5) compared to Baseline at Weeks 6 and Week 12 were significantly higher ($p=0.0002$ and $p<0.0001$, respectively) in patients treated with TCZ compared to those treated with PBO, suggesting that TCZ treatment increases insulin sensitivity.

Lymphadenopathy: At Baseline, seven (19%) PBO patients and seven (9%) TCZ had reported lymphadenopathy on physical examinations. At Week 12, of those patients who completed study Part I (i.e., did not escape or withdraw) on randomized treatment, three (18%) placebo patients and four (6%) TCZ patients had reported lymphadenopathy. Lack of sufficient patients did not enable interpretable results.

Splenomegaly: At Baseline, three (8%) placebo patients and four (5%) TCZ had reported splenomegaly in physical examinations. At Week 12, of those patients who completed study Part I (i.e., did not escape or withdraw) on randomized treatment, no PBO patients and one (1%) TCZ patient evidenced splenomegaly. Lack of sufficient patients did not enable interpretable results.

Hepatomegaly: At Baseline, six (17%) placebo patients and five (7%) TCZ patients reported hepatomegaly in physical examinations. At Week 12, of those patients who completed study Part I (i.e., did not escape or withdraw) on randomized treatment, one (6%) PBO patient and no TCZ patients reported hepatomegaly. Lack of sufficient patients did not enable interpretable results.

CHQ-PF50-Physical: At Baseline, mean CHQ-PF50 physical summary scores were comparable between the PBO (19) and TCZ (18) patients. At Week 12, of those patients who completed study Part I (i.e., did not escape or withdraw) on randomized treatment, there was a mean improvement in CHQ-PF50 physical summary scores though the improvement was greater in the TCZ patients (19) in comparison to the PBO patients (6). The CHQ-PF50 analyses are considered exploratory. The CHQ-PF50 questionnaire was specifically developed and validated for children from five to 18 years of age. Twenty-one patients (9 PBO and 12 TCZ patients) were < 5 years of age at the baseline visit and were included in the CHQ-PF50 exploratory analyses.

CHQ-PF50-Psychosocial: At Baseline, the mean CHQ-PF50 psychosocial summary scores were comparable between the PBO (41) and TCZ (42) patients. At Week 12, of those patients who completed study Part I (i.e., did not escape or withdraw) on randomized treatment, there was a mean improvement in CHQ-PF50 psychosocial summary scores but not to the extent seen in the physical summary scores. The improvement in CHQ-PF50 psychosocial summary scores was greater in the TCZ patients (7) in comparison to the placebo patients (0.4).

6.1.7 Subpopulations

Response to the primary endpoint and JIA ACR30/50/70/90 endpoints at Week 12 was

analyzed with respect to the following subgroups of Baseline characteristics:
Sex (male or female); age (2-5 years, 6-12 years, and 13-18 years); ethnicity (Hispanic and non-Hispanic); Region (Europe, North America, South America, and rest of the world); CRP (0 - < 50 mg/L and ≥ 50 mg/L); weight (<30 kgs and ≥ 30 kgs); duration of disease (< 4 years and ≥ 4 years); background oral CS dose (< 0.3 mg/kg/day and ≥ 0.3 mg/kg/day); background MTX use (yes or no); number of joints with active arthritis (0 - < 10, 10 - <30, and 30 – 71); number of joints with limitation of movement (0 - < 10, 10 - <30, and 30 – 67); fever in last 7 days (present, absent); fever in last 14 days (present, free); rash in last 14 days (present, free); previous anakinra use (yes or no) and patients with previous anakinra use and reason for discontinuation subgroups.

In the TCZ group, a higher proportion of patients responded in the following subgroups in comparison to their complement; the lower age category (more so in the harder to achieve endpoints), of Hispanic ethnicity (less so in the harder to achieve endpoints), the site located in South America (less so in the harder to achieve endpoints), weight < 30 kgs (this defines the TCZ dosing regimen and the differences in response seen between these doses), with a disease duration ≥ 4 years (more so in the harder to achieve endpoints), and with an oral CS dose of ≥ 0.3 mg/kg/day (more so in the harder to achieve endpoints). No differences in response were observed with respect to the other subgroups defined by the other Baseline characteristics.

In all categories, the JIA ACR responses were higher in the TCZ group compared to PBO. In addition, the goal of providing lighter weight patients the opportunity to attain an adequate response similar to that achieved with the heavier patients was met. In the majority of categories the patient response percentages in the TCZ 12 mg/kg group were at least as good as those achieved in the TCZ 8 mg/kg group. However, these analyses should be interpreted with caution as the study was not powered to test for differences between these subgroups. Categorizing patients into the subgroups results in lower denominators for use in the percentage calculations and, therefore, each patient was more influential.

An exploratory analysis to investigate the possible influence of patient characteristics at baseline on the probability of achieving the primary endpoint and JIA ACR30/50/70/90 endpoints at Week 12 was performed using logistic regression. The characteristics tested were weight, disease duration, background oral corticosteroid use, background MTX use, sex, age, ethnicity, region, and CRP. A step-wise model fitting approach was performed which showed that the main analysis method with adjustment for the stratification factors used at randomization was sufficient and adjustment was not required for any other covariate. In addition, the treatment by baseline characteristic interactions was tested for the primary endpoint. Of note, some interaction and subgroup analyses performed in this exploratory analysis involve small numbers of patients and, therefore, are not statistically powered or adjusted for multiplicity.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 4.4.3 Pharmacokinetics.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There was no clear trend towards higher systemic exposures (AUC2weeks, Cmin, and Cmax) in efficacy responders compared to non-responders. There was also no clear difference in mean PK exposures across responders for ACR30, 50, 70, and 90 responses. There were a similar proportion of patients (83-89%) within each exposure quartile who achieved the primary endpoint, ACR30 response and absence of fever at week 12. This indicates a lack of correlation between systemic exposure and efficacy response within the range of exposure achieved in the study. However, this data should be interpreted with caution for couple of reasons: 1) only a narrow exposure range was evaluated, and 2) there were a limited number of subjects in each systemic exposure quartile. However, it can be reasonably concluded that the range of systemic exposure estimated in the patient population following TCZ administration was sufficient to achieve the desired efficacy for the indication.

Similar to efficacy evaluation above, the sponsor conducted exposure-response analysis with safety by evaluating adverse events across systemic exposure (AUC_{2weeks}) quartiles. There was no trend towards increased incidence in Adverse Events (AEs) or Serious Adverse Events (SAEs) with increasing TCZ exposure, however, it should be noted that there are only small number of subjects in each exposure quartile to draw definitive conclusions.

6.1.10 Additional Efficacy Issues/Analyses

Logistic Regression Analyses

Table 12. WA18221 Logistic Regression Analyses

Summary of Logistic Regression Analyses of Primary Endpoint and ACR30/50/70/90 at Week 12 (ITT Population)		
	PBO N=37	TCZ N=75
JIA ACR30 + Absence of Fever	9(24%)	64 (85%)
Odds ratio (95% CI)	1	32 (9-106)
p-value	not calculated	<0.0001
JIA ACR30 Response	9 (24%)	68(91%)
Odds ratio (95% CI)	1	50 (14-186)
p-value	not calculated	<0.0001
JIA ACR50 Response	4 (11%)	64 (85%)
Odds ratio (95% CI)	1	86 (20-377)
p-value	not calculated	<0.0001
JIA ACR70 Response	3 (8%)	53 (71%)
Odds ratio (95% CI)	1	31(8-117)
p-value	not calculated	<0.0001
JIA ACR90 Response	2 (5%)	28 (37%)
Odds ratio (95% CI)	1	11 (2-53)
p-value	not calculated	0.002

Source: Adapted from WA18221 CSR, Table 34.

The proportion of responders in the TCZ group versus the PBO group for the primary endpoint and JIA ACR30/50/70/90 responses were further analyzed using logistic regression models. The models included adjustment for the Baseline stratification factors applied at randomization; weight, disease duration, background oral CS dose, and background MTX use. The results were similar to those obtained in the primary and secondary Cochran-Mantel-Haenszel analyses and showed statistically significant results in a comparison of TCZ versus placebo for all responses (Table 12).

Patients treated with TCZ were 32 times more likely to achieve the primary endpoint than patients treated with PBO (Table 12). In addition, the TCZ-treated patients were 50, 86 and 31 times more likely to achieve the JIA ACR30/50/70 responses, respectively ($p<0.0001$). For achievement of JIA ACR90, patients treated with TCZ were 11 times more likely to achieve the response than the placebo group ($p=0.002$).

The proportion of responders in the TCZ group versus the PBO group for the primary endpoint and JIA ACR30/50/70/90 responses were further analyzed using logistic regression adjusting for selected demographic and disease covariates (sex, age, ethnicity, region, and CRP) in independent models. Adjustment was also made for the Baseline stratification factors that were applied at randomization. The results were similar to those obtained in the logistic regression analysis of the primary and secondary endpoints without the inclusion of these demographic and disease covariates. There were statistically significant results in a comparison of TCZ versus

placebo for all endpoints and no differences were seen between the patient subgroups defined by the covariates.

Escape Analyses

PBO to all TCZ escape patients at Escape Baseline week comprised only 10% of the patients with a JIA ACR30 response. By Escape Week 2, patients began to have some JIA ACR responses that gradually increased in the majority of JIA ACR responses with 77% of the patients with a JIA ACR30 + absence of fever, 92% with a JIA ACR30 response, 85% with a JIA ACR50 response, 69% in JIA ACR70 response and 54% in JIA ACR90 response by Escape Week 10. Overall, placebo to TCZ 8 mg/kg escape patients had a higher percentage of all responses, except for JIA ACR70, than the placebo to TCZ 12 mg/kg escape patients. Patient 1663, a 10-year-old male randomized to TCZ 8 mg/kg who escaped to TCZ 8 mg/kg escape on Day 31 did not have any JIA ACR30 + absence of fever and JIA ACR30/50/70/90 responses at the end of Part I. This patient entered escape inadvertently as the investigator initially suspected MAS that was later found to be LFT elevations.

Supportive Efficacy Results

Supportive efficacy results from Phase II Chugai sJIA studies are as follows:

- Study MRA316JP (N=56 randomized who received >/=1 dose):
  At the end of 6 week open-label induction, JIA ACR30/50/70 was achieved by 52(91%), 48(86%) and 38(68%). 44 subjects entered double blind withdrawal maintenance. The primary endpoints of JIA ACR30 and CRP<15 mg/L were achieved by 17% of placebo versus 80% of TCZ subjects, with a significant p value <0.0001.
- Study MRA317JP (N=60)
  This study was an open label extension for MRA011JP or MRA316JP responders in which JIA ACR30 response was achieved in 89% after 12 wks, then 86% to 100% from 24 to 324 wks after treatment start. JIA ACR50 response was achieved in 85% after 12 weeks, 93% after 24 wks, and then 85 to 100% after the start of treatment. A JIA ACR70 response was achieved in 72% after 24 wks and in 71-100% 36 to324 weeks after the start of treatment. In addition, 70% reduction of CS doses was achieved by 50% of subjects.
- Study MRA324JP (N=82).
  This study was a long-term, open-label study initiated to provide expanded access to TCZ for patients with sJIA in Japan who were showing resistance to existing treatments. In this study, ACR30 was achieved in 59% after 12 wks, and then in 56% to 80% from 24 to 120 weeks after the start of treatment. JIA ACR50 response was achieved in 55% after 12 weeks and in 59% after 24 weeks, and then in 33% to 79% from 36 to 120 weeks after treatment start. JIA ACR70 response was achieved in 36% of subjects after 12 weeks and 44% after 24 weeks, and then ranged from 33% to 71% from 36 to 120 weeks after treatment start. In addition, a CS decrease of ≥ 50% increased until about one year after the start of treatment and remained at over 70%.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The primary source of safety data is from pivotal study WA18221, with supportive data provided from the four clinical multi-dose studies in the Chugai clinical program (see Section 7.1.3 below).

7.1.2 Adequacy of Data

Overall, the safety coding and safety datasets and tabulations were adequate to enable review. Verbatim terms were mapped to MedDRA terms and coding dictionaries provided.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

In this submission, safety data from study WA18221 were summarized for the first 12 weeks of controlled treatment (part 1 of the study), so that the safety and tolerability of TCZ is presented compared with the placebo. All safety data from all patients when 50 of all patients completed at least 1 year of treatment in part 2 of WA18221 (May 10, 2010) were also summarized in order to provide safety information on the longer-term use of TCZ in sJIA patients.

Safety data from the Chugai sJIA studies were provided to support safety data from the pivotal study WA18221. Because of the differences in sJIA patient population, study design, study conduct, and safety assessment and analysis between study WA18221 and Chugai sJIA studies, data from the Chugai sJIA studies were not pooled with the data from the pivotal study WA18221, and were summarized separately as supporting safety.

The presentation for the TCZ safety data in the Chugai sJIA studies focused on the multi-dose studies of TCZ in patients with sJIA, with the emphasis on the long-term treatment effect of TCZ on safety for sJIA patients. Therefore, the safety data from the four multi-dose studies, MRA011JP, MRA316JP, MRA317JP, and MRA324JP, were not presented in the summary, and data from study LRO32, a single ascending-dose study, are not included.

7.1.4 Safety in WA18221 Escape Patients

According to protocol WA18221, patients meeting protocol specific criteria during study treatment in part 1 were permitted to switch to open-label TCZ treatment, and these patients were designated as escape patients.

The safety data summaries contained in this submission included data from escape patients prior to the first time they qualified for escape and started to receive escape therapy. For the analysis of part 1 of the study, once a patient started receiving escape therapy, data were excluded from the safety data summaries from that time point onward, i.e., the patient was censored at the time of escape. In the clinical safety summary, for the first 12 weeks of controlled treatment in study WA18221, data collected after escape were presented separately in and are summarized in Section 7.5.6 of this review. All patient listings included data both prior to and after escape, with a flag indicating assessments performed while on escape therapy. In the May 10th 2010 cut for long-term extension data, all data from the time of first TCZ infusion (including escape) were presented.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 13. WA18221 Summary of Study Duration and Treatment Exposure May 10, 2010 Cutoff

Study WA18221 Safety Population: Summary of Study Duration and Treatment Exposure May 10, 2010 Data Cutoff					
	TCZ 8 mg/kg N=52	TCZ 12 mg/kg N=50	TCZ 8 to 12 mg/kg N=1	TCZ 12 to 8 mg/kg N=9	TCZ ALL N=112
Study Duration in Weeks Mean (SD)	64(17)	60(17)	69	59(16)	62(17)
Study Duration in Years Mean (SD)	1.3(0.3)	1.1 (0.3)	1.3	1.2 (0.3)	1.2 (0.3)
Trial Treatment Exposure in Weeks	64(18)	60(18)	70	59(16)	62(18)
Trial Treatment Exposure in Years	1.2(0.4)	1.1(0.4)	1.3	1.1(0.2)	1.2(0.3)
Number TCZ Infusions Received					
1 to 5	1(2%)	2(4%)	0	0	3(3%)
11 to 15	1(2%)	2(4%)	0	0	3(3%)
16 to 20	5(10%)	2(4%)	0	2	9(8%)
21 to 25	9(17%)	12(24%)	0	3	24(21%)
26 to 30	14(27%)	14(28%)	0	1	29(26%)
31 to 35	6(12%)	9(18%)	1	2	18(16%)
36 to 40	9(17%)	7(14%)	0	1	17(15%)
41 to 45	6(12%)	1(2%)	0	0	7(6%)
46 to 50	1(2%)	0	0	0	1(<1%)
52 to 55	0	1(2%)	0	0	1(<1%)

N represents number of patients contributing to summary statistics
Duration in study (weeks) = (date of last assessment – date of first TCZ dose +1 / 7).
Duration in study (years) = (date of last assessment – date of first TCZ dose +1) 365.25).
Exposure to trial treatment (weeks) = (date of last dose – date of first TCZ dose +15 / 7).

Exposure to trial treatment (years) = (date of last dose – date of first TCZ dose +15 / 365.25).
Sum is across all patients in the treatment arm.
Source: Adapted from Summary of Clinical Safety, Tables 5 and 6.

The summary of study WA18221 study duration and treatment exposure to the May 10, 2010 data cut is illustrated in Table 13 above. Mean study duration and trial treatment exposure in the all TCZ population was 1.2 +/- 0.3 years. 78% of patients received between 16 to 40 TCZ infusions.

7.2.2 Explorations for Dose Response

Refer to section 6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations and section 7.5.1 Dose Dependency for Adverse Findings.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was considered necessary to further explore the safety profile of tocilizumab, which is primarily based on human clinical data.

7.2.4 Routine Clinical Testing

The type and frequency of routine clinical testing of patients in the 5 pivotal studies and long term extensions was adequate. For details, see section 9.4 Individual Study Reports.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

TCZ, is the only approved IL-6 inhibitor in class. If approved, TCZ will be the first agent
indicated for the treatment of sJIA. The safety data submitted were also evaluated terms of what is known regarding the safety profile of TCZ in RA. In addition, the data were evaluated in the context of what is known regarding the safety profile of approved biologic agents for RA, to include TNF inhibitors, rituximab, anakinra, and abatacept.

7.3 Major Safety Results

Table 14. Major AE Findings: Study WA18221 vs Chugai sJIA Studies

Summary of Major AE Findings Study WA18221 and Chugai sJIA Studies		
Description	**Study WA18221**	**Chugai sJIA Studies**
AE		
overall incidence AE	98.00%	100%
overall rate AE	859 per 100 pt-yrs	779 per 100 pt-yrs
SAE		
overall incidence SAE	22%	42%
overall rate SAE	25 per 100 pt-yrs	32 per 100 pt-yrs
Infection		
overall incidence AE	89%	91%
overall rate AE	307 per 100 pt-yrs	381 per 100 pt-yrs
overall incidence SAE	13%	N/A
overall rate SAE	11 per 100 pt-yrs	13 per 100 pt-yrs
MAS	3% (3 patients)	3% (4 patients)
Neutropenia AE		
overall incidence AE	18%	12%
overall rate AE	11.3 per 100 pt-yrs	7 per 100 pt-yrs
Duodenal Perforation	0	1 patient
Anaphylaxis by Sampson's analysis	< 1 % (1 patient)	0
Death		
overall incidence	0.9% (1 patient)	1% (2 patients)
overall rate	0.8 per 100 pt-yrs	0.6 per 100 pt-yrs
Premature Treatment Withdrawals for AE		
overall incidence	4%	7%
overall rate	3 per 100 pt-yrs	3 per 100 pt-yrs

WA18221 Week 12 data
Source: Summary of Clinical Safety, Table 14.

An overview of the major AE findings in study WA18221 (controlled data up to Week 12) and the Chugai sJIA pooled studies is provided in Table 14 above. As presented, both populations exhibited similar incidence and rate of AEs, although the overall rate of SAE, infection AE and infection SAE were higher in the Chugai sJIA group.

7.3.1 Deaths

A total of 9 deaths were reported, 1 in study WA18221, 2 in Chugai sJIA studies, 3 in the post marketing program, 1 in the Roche TCZ compassionate use program, and 2 in the TCZ compassionate use program in Japan. Brief narratives of all deaths are as follows:

Patient 1324, 16 years old, male, the reason of death: suspected tension pneumothorax (study WA18221)
This patient had sJIA of 13 years duration and was randomized to TCZ 12 mg/kg in study WA18221 April 14, 2009. The patient completed Part 1 of the study subsequently entered Part 2. On study (b) (6), the patient developed viral gastroenteritis with fever that resolved after one

day. On study (b) (6) he developed increasing dyspnea and died on arrival to the hospital. No autopsy or radiographic studies were performed. The diagnosis of pneumothorax was based primarily on the clinical history and the presence of air coming out of the intercostal needle during initial resuscitative efforts in the emergency room. There were no reports of fracture or trauma prior to the event. The last dose of study medication prior to the event was study (b) (6).

Patient 2101, 3 year old female; cause of death: development of MAS (Study MRA324JP)
Patient 2101 was receiving TCZ 8 mg/kg every 2 weeks. She required high dose corticosteroids (> 1.0 mg/kg) for disease control and had associated complications such as corticosteroid-induced osteoporosis, hypertension and obesity. On study (b) (6) she developed rotavirus enteritis with elevated ALT (405 I/U) and AST (168 I/U). TCZ was suspended per protocol. From study Day 56 to 70, her disease activity worsened and progressed to MAS; intravenous dexamethasone was administered on (b) (6). On (b) (6), she developed precordial purpura and gross hematuria. Labs revealed elevated WBC (32,700/μL), decreased platelets (8.0 x 10E4/μL), elevated AST (1743 UI/L) and ALT (797 IU/L), elevated LDL (10,594 IU/L), and elevated ferritin (1219 ng/mL). Urine B2-MG was elevated at 72,390 μg/L. Preparations were made to administer cyclosporine. However the patient lost consciousness and experienced respiratory and cardiac arrest. Resuscitative events were not successful. Blood cultures drawn on study (b) (6) were negative for bacteria and fungi.

Patient 3001, 22 year old male; cause of death: arrhythmia caused by cardiac amyloidosis. (Study MRA324JP)
Patient 3001 was found dead (b) (6) days after the 7th infusion of TCZ. He was diagnosed with sJIA at 14 years of age and had added significant medical history of severe diarrhea, splenomegaly and pericarditis. Lip biopsy performed prior to TCZ treatment showed amyloid deposition, which together with high SAA values and chronic gastrointestinal disorders suggested systemic amyloid deposition. With TCZ treatment he evidenced improvements in systemic inflammation (fever, CRP elevation etc.) as well as gastrointestinal symptoms (diarrhea). There were no notable findings prior to his death. Autopsy findings revealed systemic deposition of amyloid including heart (conductive system) and myocarditis most likely associated with the primary disease. It was concluded that the patient died due to arrhythmia caused by cardiac amyloidosis.

Patient MCN 588086, 22 month-old female with sJIA; cause of death: acute respiratory distress syndrome (JPMS sJIA Program)
The medical history was significant for premature birth, low birth weight, and multiple congenital anomalies, including cleft palate, severe imbalance between the head and body, cleft and short fingers, hypoplastic kidney, and suspected Ectrodactyly-ectodermal dysplasia-clefting syndrome. She required mechanical ventilation at birth and for an unspecified time thereafter. She developed hypertension secondary to the hypoplastic kidney.

sJIA was diagnosed at approximately one year of age and was uncontrolled by steroid therapy (oral and intravenous pulse). TCZ was initiated on September 2, 2008. Her treatment course from September 2008 to January 2009 was

complicated by multiple exacerbations of chronic bronchitis, anaphylaxis (2 hours after second infusion), gastroenteritis, hypercoagulation, acute renal failure, and post-infusion fevers, one episode of ARDS (resolved March 2009), pulmonary edema (improved May 2009). TCZ infusions were held during the acute infections. On (b) (6) she developed pneumonia, followed by a second episode of ARDS. The patient expired despite intubation, cardiac massage and cardiotonic medications. No autopsy was performed.

MCN 624762: a 4 month-old male with sJIA; cause of death: pseudomonas sepsis (JPMS sJIA Program).

The patient's medical history included anaemia, DIC, serum ferritin increased, hepatomegaly, parenteral nutrition, MAS (diagnosed by bone marrow aspirate), thrombocytopenia, pyrexia, rash, skin necrosis (fingertips), and leukopenia.

On January 13, 2009 the first dose of TCZ was infused. (b) (6) later, he experienced pancytopenia. Following transfusion, on (b) (6) he received a second TCZ infusion. His skin necrosis worsened and by (b) (6) had extended to the four limbs, cheeks, eyelids, oracle, and the nasal root bilaterally. He had an increased respiratory rate, reduced oxygen saturation and difficulty expectorating sputum but his CXR did not show any infiltration. Two additional doses of TCZ were administered on January 28 and February 4, 2009. TCZ was discontinued (b) (6) due to marked pancytopenia and azathioprine started for disease control. Pseudomonas aeruginosa was cultured from the patient's sputum on (b) (6) Steroid pulse therapy was initiated for interstitial pneumonia. On (b) (6), his blood pressure decreased and did not respond to vasopressors and he died of a pseudomonas infection/sepsis. An autopsy was not performed.

MCN 678197: a 45 year-old male receiving TCZ for AOSD reported from the RELACIONAR surveillance program; cause of death: multi-organ Failure (JPMS sJIA Program).

The patient had previously received rituximab for Still's disease. On June 14, 2009, the patient received a single dose of TCZ 8mg/kg for Still's disease however, due to financial reasons he did not receive further doses. In (b) (6) 2009 the patient developed several episodes of diarrhea associated with fever and dehydration requiring hospitalization and treatment with ciprofloxacin and metronidazole.

On October 2, 2009, the patient was re-started on TCZ 8 mg/kg/month and received further doses on November 3 and December 3, 2009. On an unknown date the patient became anuric with an un-recordable blood pressure. Subsequently, he developed generalized edema and multi-organ failure. TCZ was administered on January 4, 2010 and on (b) (6) the patient died due to sepsis secondary to toxic megacolon and multi-organ failure. The reporter postulated that the sepsis could have been caused by resistant clostridium infection. At the time of his death, diarrhea had worsened and pain was persisting. There was no information about an autopsy.

Case 359503: 5 year old female with juvenile RA; compassionate use case; cause of death: acute myeloid leukemia (AML)

The patient had a history of juvenile RA since April 1999. On July 6, 2001, the patient began IV TCZ therapy which continued until February 2, 2004. On April 25, 2002 she was started on cyclophosphamide pulse therapy for interstitial pneumonia; receiving 12 courses from May 2002 to September 2003. In November 2002 she was started on oral thalidomide and in July 2003 oral cyclosporine was restarted. On (b) (6) she was diagnosed with AML (fab classification: m4) after bone marrow biopsy. On February 10, 2004, she developed fever unresponsive to antibiotic therapy, two weeks later steroid therapy was increased without effect. On (b) (6), she received IV TCZ at for disease flare. On (b) (6) her heart rate decreased from 150-160 beats per minute to 70. Echocardiograpy revealed pulmonary hypertension believed secondary to interstitial pneumonia. That evening, she experienced vomiting, acute increase in blood blast cells, convulsions and unconsciousness. She died the next day. The cause of death was reported as cardiac failure due to acute myeloid leukemia and respiratory failure. It was felt that that her AML was secondary and induced by cyclophosphamide.

Case 397961, 4 year old female with sJIA; cause of death: DIC due to disease progression

The patient had responded poorly to multiple drugs and had experienced adverse drug reactions. According to the investigator, TCZ was used as a last rescue treatment. On (b) (6), the patient's systolic blood pressure temporarily increased to over 200 mmHg. Her systemic condition worsened but her blood pressure stabilized. Her pupils were dilated and she had severe inflammatory symptoms. She received a single dose of IV TCZ 8 mg/kg. The next evening, her systolic blood pressure decreased to 50 mmHg, her systemic inflammatory condition appeared to be uncontrolled and her CRP increased. Her systolic blood pressure decreased further and did not improve despite treatment.

Cardiac massage was unsuccessful. The cause of death was worsening of sJIA and bleeding due to DIC.

MCN 349156, 52 year old male with adult Still's disease; cause of death: cardiac failure secondary to chronic cardiomyopathy

This case was received from Chugai Pharmaceutical Co Ltd. The patient had received 2 doses of TCZ: 1mg/kg on June 27, 2000, and 5mg/kg on July 4, 2000. The second dose was given approximately (b) (6) prior to the patient's death. The patient had longstanding complaints of shortness of breath but clinically this was thought to be due to panic attacks as it was paroxysmal and associated with parasthesia of the face and hands. Sequential x-rays taken in June 2000 due to development of lower extremity edema demonstrated mild cardiomegaly but no other evidence of cardiac failure and he was prescribed furosemide. He became hypotensive on (b) (6) and was initially treated with broad spectrum antibiotics. His condition deteriorated however, and he died on (b) (6). Microbiological cultures were all negative. Post mortem examination showed a diffuse dilated cardiomyopathy. The coronary arteries showed no evidence of atheroma and there was no evidence of infection.

7.3.2 Nonfatal Serious Adverse Events

Table 15. Summary of SAE: Week 12 vs May 10, 2010 Data Cutoff

Summary of SAE by Body System, Preferred Term and Trial Treatment- Week 12 vs May 10, 2010 Cutoff (WA18221 Safety Population)					
BodySystem/AE	TCZ 8 mg/kg N=52 No./%	TCZ 12 mg/kg N=50 No./%	TCZ 8 to 12 mg/kg N=1 No./%	TCZ ALL Wk 12 N=112 No./%	TCZ May 10 N=112 No./%
ALL BODY SYSTEMS					
Total Pts with at Least one AE	0	1(3)	2(5)	3(4)	25(22)
Total Number AE	0	1	3	4	32
INFECTIONS AND INFESTATIONS					
Total Pts with at Least one AE	0	1(3)	1(3)	2(3)	15(13)
Bacterial Arthritis	0	1(3)	0	1(1)	1(1)
Varicella	0	0	1(3)	1(1)	3(3)
Total Number AE	0	1	1	2	15
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
Total Pts with at Least one AE	0	0	1(3)	1(1)	1(1)
Angioedema	0	0	1(3)	1(1)	1(1)
Urticaria	0	0	1(3)	1(1)	1(1)
Total Number AE	0	0	2	2	2

Source: Summary of Clinical Safety, Tables 19 and 21..

Table 15summarizes Week 12 versus May 10, 2010 cutoff data of SAEs occurring in study WA18221. The most common SAEs occurring during both the placebo-controlled study and LTE were infectious in nature (bacterial arthritis and varicella).

Table 16. WA18221 Summary of SAE May 10, 2010 Data Cut

Summary of SAE by Body System, Preferred Term and Trial Treatment- May 10, 2010 Data Cut (Study WA18221 Safety Population)					
Adverse Event	TCZ 8 mg/kg No./%	TCZ 12 mg/kg No./%	TCZ 8 to 12 mg/kg No./%	TCZ 12 to 8 mg/kg No./%	TCZ ALL N=112 No./%
All Body Systems					
Total Pts @ least 1 AE	9(17)	14(28)	0	2	25(22)
Total Number AEs	12	17	0	3	32
Infections and Infestations					
Total Pts @ least 1 AE	5(10)	9(18)	0	1	15(13)
Gastroenteritis	1(2)	2(4)	0	0	3(3)
Varicella	0	2(4)	0	1	3(3)
Pheumonia	0	2(4)	0	0	2(2)
Bacterial Arthritis	1(2)	0	0	0	1(1)
Bronchopneumonia	1(2)	0	0	0	1(1)
Viral Gastroenteritis	0	1(2)	0	0	1(1)
Herpes Zoster	0	1(2)	0	0	1(1)
Otitis Media	1(2)	0	0	0	1(1)
Pharyngotonsillitis	1(2)	0	0	0	1(1)
Upper Respiratory Tract Infection	0	1(2)	0	0	1(1)
Total Number AEs	5	9	0	0	15
Injury/Poisoning/Procedural					
Total Pts @ least 1 AE	2(4)	2(4)	0	0	4(4)
Femur fracture	0	1(2)	0	0	1(1)
Forearm Fracture	0	1(2)	0	0	1(1)
Fracture	1(2)	0	0	0	1(1)
Joint Dislocation	1(2)	0	0	0	1(1)
Total Number AEs	5	9	0	0	4
Neoplasme					
Total Pts @ least 1 AE	1(2)	1(2)	0	1	3(3)
Histiocytosis Haematophagic	1(2)	1(2)	0	1	3(3)
Total Number AEs	1	1	0	1	3

Table 16. WA18221 Summary of SAE May 10, 2010 Data Cut (continued)

Summary of SAE by Body System, Preferred Term and Trial Treatment- May 10, 2010 Data Cut (Study WA18221 Safety Population)					
Adverse Event	TCZ 8 mg/kg N=52 No./%	TCZ 12 mg/kg N=50 No./%	TCZ 8 to 12 mg/kg N=1 No./%	TCZ 12 to 8 mg/kg No./%	TCZ ALL N=112 No./%
Respiratory, Thoracic and Mediastinal Disorders					
Total Pts @ least 1 AE	1(2)	0	0	1	2(2)
Pneumothorax	0	0	0	1	1(1)
Pulmonary Veno-Occlusive Dz	1(2)	0	0	0	1(1)
Total Number Aes	1	0	0	1	2
Skin and SQ Disorders					
Total Pts @ least 1 AE	0	1(2)	0	0	1(1)
Angioedema	0	1(2)	0	0	1(1)
Urticaria	0	1(2)	0	0	1(1)
Total Number AEs	0	2	0	0	2
Cardiac Disorders					
Total Pts @ least 1 AE	1(2)	0	0	0	1(1)
Cardiac Failure	1(2)	0	0	0	1(1)
Total Number AEs	1	0	0	0	1
Gastrointestinal Disorders					
Total Pts @ least 1 AE	0	1(2)	0	0	1(1)
Gastritis	0	1(2)	0	0	1(1)
Total Number AEs	0	1	0	0	1
Genl D/O and Admin Site Conditions					
Total Pts @ least 1 AE	0	1(2)	0	0	1(1)
Influenza-like Illness	0	1(2)	0	0	1(1)
Total Number AEs	0	1	0	0	1
Hepatobiliary Disorders					
Total Pts @ least 1 AE	1(2)	0	0	0	1(1)
Hypertransaminasemia	1(2)	0	0	0	1(1)
Total Number AEs	1	0	0	0	1
Investigations					
Total Pts @ least 1 AE	1(2)	0	0	0	1(1)
Transaminases Increased	1(2)	0	0	0	1(1)
Total Number AEs	1	0	0	0	1
Metabolism and Nutrition Disorders					
Total Pts @ least 1 AE	0	1(2)	0	0	1(1)
Dehydration	0	1(2)	0	0	1(1)
Total Number AEs	0	1	0	0	1

Investigator text for Adverse Events encoded using MedDRA version 13.0
Percentages are based on N. Percentages not calculated if N<10.
Multiple occurrences of the same adverse event in one individual only counted once.
Data on Placebo treatment from study part I is excluded.
Source: Adapted from Summary of Clinical Safety, Table 21.

As shown in Table 16 above, the most common SAEs occurring in the WA18221 safety population were Infections and Infestations (13%), followed by neoplasms (all MAS, 2%). The SAEs of angioedema, urticaria, cardiac failure, gastritis and influenza-like illness occurred in one patient each (1%). Infection SAEs were more frequent in the TCZ 12 mg/kg group (18%) than the TCZ 8 mg/kg group (10%).

Table 17. SAE with a Rate >0.5 per 100 Pt-yrs Chugai sJIA Studies, Safety Population

Summary of SAE Reported at a Tate of >5 Per 100 Patient-Years, Chugai sJIA Studies, Safety Population						
	011/316/317JP N=67		324JP N=82		All Exposure N=149	
Total TCZ Exposure	228.0 PY		93.3PY		326.3PY	
Preferred Term	N	[p100pt yr]	N	[p100pt yr]	N	[p100pt yr]
Gastroenteritis	12	[5.3]	3	[3.1]	15	[4.6]
Pneumonia	7	[3.1]	1	[1.0]	8	[2.5]
Juvenile arthritis	4	[1.8]	4	[4.1]	8	[2.5]
Alanine aminotransferase increased	5	[2.2]	1	[1.0]	6	[1.8]
Aspartate aminotransferase increased	5	[2.2]	1	[1.0]	6	[1.8]
Cataract operation	4	[1.8]	2	[2.0]	6	[1.8]
Histiocytosis haematophagic	0	[0]	4	[4.1]	4	[1.2]
Cataract	1	[0.4]	3	[3.1]	4	[1.2]
Inguinal hernia	2	[0.9]	1	[1.0]	3	[0.9]
Infusion related reaction	0	[0]	3	[3.1]	3	[0.9]
Bronchitis	2	[0.9]	0	[0]	2	[0.6]
Cellulitis	2	[0.9]	0	[0]	2	[0.6]
Nasopharyngitis	2	[0.9]	0	[0]	2	[0.6]
Subcutaneous abscess	2	[0.9]	0	[0]	2	[0.6]
Urinary tract infection	0	[0]	2	[2.0]	2	[0.6]
Anaphylactoid reaction	2	[0.9]	0	[0]	2	[0.6]
Enterocolitis	1	[0.4]	1	[1.0]	2	[0.6]
Gastrointestinal haemorrhage	1	[0.4]	1	[1.0]	2	[0.6]
Ileus	2	[0.9]	0	[0]	2	[0.6]
Hepatic function abnormal	2	[0.9]	0	[0]	2	[0.6]
Arthralgia	2	[0.9]	0	[0]	2	[0.6]
Arthritis	2	[0.9]	0	[0]	2	[0.6]
Nephrolithiasis	0	[0]	2	[2.0]	2	[0.6]

Source: Summary of Clinical Safety, Table 22.

In the all exposure population of the Chugai sJIA studies, a total of 62 patients (42%) reported 105 SAEs over a median treatment duration of 2.1 years (32 per 100 patient-years). The above Table 17 summarizes SAEs in the pooled Chugai sJIA study data. The most frequent SAEs were those in Infections and Infestation (13.2 per 100 patient-years, most commonly gastroenteritis [4.6 per 100 patient-years] and pneumonia [2.5 per 100 patient-years]), Musculoskeletal and Connective Tissue Disorders (4.3 per 100 patient-years, most commonly juvenile arthritis-disease flare [2.5 per 100 patient-years]). Other frequent individual SAEs included ALT increased and AST increased (1.8 per 100 patient-years each), cataract operation (1.8 per 100 patient-years) and cataract (1.2 per 100 patient-years), and MAS (1.2 per 100 patient-years). The rate of all other SAEs was < 1.0 per 100 patient-years.

Two SAEs were reported in study MRA316JP, both during the open-label treatment phase. None were reported during the double-blind treatment phase. The 2 SAEs were anaphylactoid symptoms in 1 patient and gastrointestinal hemorrhage in another patient.

7.3.3 Dropouts and/or Discontinuations

Table 18. WA18221 Line Listing of Patients Withdrawn for AE

WA18221 Listing of Patients Withdrawn for AE; Week 12 and May 10, 2010 Data Cutoff								
AE to Week 12								
Treatment	**Adverse Event**	**Age (yr)**	**Sex**	**Race**	**Weight (kg)**	**Intensity**	**Day Onset**	**Outcome**
PBO N=36	MAS	8	F	White	26	severe	70	Unknown
TCZ 12 mg/kg N=38	Angioedema	13	M	White	13	Life threatening	57	resolved
AE to May 10, 2010 Cutoff								
Treatment	**Adverse Event**	**Age (yr)**	**Sex**	**Race**	**Weight (kg)**	**Intensity**	**Day Onset**	**Outcome**
TCZ 8 mg/kg N=52	ALT Increased	12	F	White	42	mild	15	Unresolved
TCZ 8 mg/kg N=52	Pulmonary Embolism	15	F	White	54	Life threatening	388	Unresolved
TCZ 12 mg/kg N=50	Angioedema	3	M	White	13	Life threatening	57	resolved
TCZ 12 mg/kg N=50	MAS	25	F	White	25	severe	56	resolved

Source: Summary of Clinical Safety, Table 23 and 24.

Table 18 provides a line listing of WA18221 subjects withdrawn for AEs. One subject in the TCZ 12 mg/kg group was withdrawn during the placebo-controlled part of the study for angioedema. In Part II, two subjects from the TCZ 8 mg/kg group were withdrawn; one for ALT elevation (mild) and one for pulmonary embolism (life threatening). Two subjects from the 8 mg/kg group were also withdrawn: one for angioedema (life threatening) and one for MAS (severe).

In the all exposure Chugai sJIA study population, ten patients (7%) were withdrawn from study treatment for AEs. In studies MRA011JP/MRA316JP/MRA317JP, six patients (9%) were withdrawn from study treatment for AEs. Anaphylactoid reaction resulted in treatment withdrawals in two patients. Duodenal perforation, gastrointestinal hemorrhage, herpes zoster, and ALT increase each accounted for withdrawal in individual patients. All AEs resolved after study treatment withdrawal.

In study MRA324JP, four patients (5%) were withdrawn from study treatment for AEs. AEs resulting withdrawal included infusion related reaction (2 patients), MAS (1 patient), and cardiac amyloidosis (1 patient).

7.3.4 Significant Adverse Events

Based on the known safety profile of TCZ in RA patients, in addition to previously identified risks of TCZ in sJIA patients (based on sJIA Chugai studies), primary AEs of interest included infections, macrophage activation syndrome (MAS), neutropenia, liver function test abnormalities, anaphylaxis and gastrointestinal perforation.

<u>Infection</u>

Table 19. Summary of Infection AE >5%

Summary of Infection AE >5% by Body System, Preferred Term and Trial Treatment- May 10, 2010 Data Cut (WA18221 Safety Population)					
Summary of Infection AE by Body System, Preferred Term and Trial	TCZ 8 mg/kg N=52 No./%	TCZ 12 mg/kg N=50 No./%	TCZ 8 to 12 mg/kg N=1 No./%	TCZ 12 to 8 mg/kg N=9 No./%	TCZ ALL N=112 No./%
ALL BODY SYSTEMS					
Total Patient with at Least 1 AE	46(89)	44(88)	1(100)	9(100)	100(89)
Total Number of AEs	102	146	2	23	273
INFECTIONS AND INFESTATIONS					
Total Patient with at Least 1 AE	44(85)	43(86)	1(100)	9(100)	97(87)
Nasopharyngitis	14(27)	14(28)	0	5(56)	33(30)
Upper Respiratory Infection	14(27)	17(34)	0	1(11)	32(29)
Rhinitis	2(4)	8(16)	0	0	11(10)
Ear Infection	6(11)	13(26)	0	0	19(17)
Viral Gastroenteritis	3(6)	6(12)	0	1(11)	10(9)
Gastroenteritis	4(8)	4(8)	0	1(11)	9(8)
Impetigo	1(2)	6(12)	1(100)	0	8(7)
Viral Infection	3(6)	4(8)	0	1(11)	8(7)
Viral Upper Respiratory Infection	5(10)	2(4)	0	1(11)	8(7)
Bronchitis	2(4)	4(8)	0	0	6(5)
Pharyngitis	4(8)	1(2)	0	1(11)	6(5)
Cellulitis	0	4(8)	0	0	4(4)
Sinusitis	3(6)	1(2)	0	0	4(4)
Urinary Tract Infection	3(6)	1(2)	0	0	4(4)
Varicella	0	3(6)	0	1(11)	4(4)
GASTROINTESTINAL DISORDERS					
Total Patient with at Least 1 AE	11(21)	10(20)	0	0	21(19)
Diarrhea	11(21)	6(12)	0	0	17(15)
Dental Caries	0	4(8)	0	0	4(4)
EYE DISORDERS					
Total Patient with at Least 1 AE	1(2)	4(8)	0	1(11)	6(5)
Conjunctivitis	1(2)	4(8)	0	1(11)	6(5)

Source: Summary of Clinical Safety stae11, pages 289-291.

As shown in Table 19 above, 97 patients treated with TCZ (87%) reported 247 AEs under the system organ class of Infections and Infestations. This gave an AE rate of 280 per 100 patient-years. The incidence of Infection and Infestation AEs was similar in the two TCZ dosing groups (85% vs 86%) while the rate of these AEs was lower in the TCZ 8 mg/kg group (201 per 100 patient-years) than in the TCZ 12 mg/kg group (374 per 100 patient-years).

The most frequent AEs under the system organ class of Infections and Infestations were nasopharyngitis (30% and 56 per 100 patient-years) and upper respiratory tract infection (29% and 52 per 100 patient-years). The incidence and rate of many frequent AEs such as upper respiratory tract infection, rhinitis, ear infection, gastroenteritis viral, impetigo, and bronchitis were lower in patients with TCZ 8 mg/kg than those with TCZ 12 mg/kg. This difference in incidence and rate of frequent infection AEs may have been a reflection of the different baseline characteristics between the patients in the <30 kg group versus the ≥ 30 kg group with the <30 kg patients being younger, more receiving MTX and receiving a higher mean dose of corticosteroids at baseline than ≥ 30 kg patients (see Section 6.1.2, Demographics).

The majority of AEs under the system organ class of Infections and Infestations were mild or moderate in intensity, and only 4 out of a total of 247 such AEs were considered severe, which

were gastroenteritis, varicella, bacterial arthritis, and pharyngotonsillitis, each of these 4 events being reported in one of 4 different patients.

As shown in Table 16, 15 SAEs in the system organ class of Infections and Infestations were reported (13%). This represented an event rate of 11 per 100 patient-years. All SAEs occurred as single events in 1 patient except for gastroenteritis (3 patients), varicella (3 patients), and pneumonia (2 patients).

Macrophage Activation Syndrome

Table 20. WA18221 Safety Population Line Listing of Patients with Macrophage Activation Syndrome AE

Listing of Patients with Macrophage Activation Syndrome Adverse Events by Trial Treatment (Study WA18221, Safety Population)									
First 12 Weeks Controlled Treatment									
TREATMENT	Age (yr)	Sex	Race	Weight (kg)	Intensity	Day Onset	Duration (days)	Outcome	Effect on Treatment
Tcz 12 mg/kg	8	F	white	26	severe	70	114	resol- no seq	discontinued
May 10, 2010 Data Cut									
TREATMENT	Age (yr)	Sex	Race	Weight (kg)	Intensity	Day Onset	Duration (days)	Outcome	Effect on Treatment
Tcz 8 mg/kg	15	F	white	54	life threat	397	8	resol- no seq	dose mod/interrupted
Tcz 8 mg/kg	8	F	white	25	severe	56	45	resol- no seq	discontinued
Tcz 12 to 8 mg/kg	4	M	white	25	moderate	19	18	resol- no seq	dose mod/interrupted

Source: Summary of Clinical Safety Table 29 and Page 107.

Table 20 above provides a line listing of WA18221 study subjects who experienced MAS. In the 12 Week controlled trial, one escape patient in the TCZ 12 mg/kg group experienced severe MAS. In the long-term extension period, as of the May 2010 data cut, two patients in the TCZ 8 mg/kg group and one patient in the 12 mg/kg to 8 mg/kg group had MAS. In all four patients, the event resolved without sequelae.

MAS was reported in 4 patients in the all exposure population (2.7%). These cases tended to be in younger patients and all were in females with a body weight < 30 kg. The disease durations varied but all these cases were considered as having severe sJIA disease because all received oral corticosteroids at doses ≥ 1 mg/kg/day at Baseline. None had a history of MAS prior to the study participation.

In the Chugai Japan studies, of the 4 patients, all in study MRA324JP, who developed MAS during study treatment, 1 patient had a fatal outcome due to the development of MAS and the other 3 patients were successfully treated with intravenous corticosteroids and/or cyclosporine and continued TCZ treatment after resolution of the event. There were potential triggering events such as infections or changes in treatment (steroid tapering) preceding the occurrence of MAS. In 2 of the 4 reported cases, the diagnosis was not definite and thus the event was reported as suspected MAS.

A panel of 3 clinical experts with backgrounds in pediatrics and/or rheumatology, and with a specialist interest in MAS was established and met as required to discuss and adjudicate all cases

of potential MAS (from Chugai clinical studies: MRA316JP, MRA317JP, MRA324JP, and JPMS cases). Potential MAS cases were identified from the Roche safety database as those cases with a reported event term of MAS, or disease flare with accompanying ALT/AST elevations for the indications of juvenile arthritis and adult onset Still's disease.

Following adjudication, the 23 events (in 21 patients) reported as MAS or other reported terms and the 6 events (in 6 patients) reported as disease flare with ALT/AST elevations were assessed as follows:

- Definite MAS: 10 events
- Potential MAS: 9 events
- Not MAS: 6 events
- Insufficient data to make a decision: 4 events

Of the 23 events (in 21 patients) that were reported as either MAS or other reported terms, 21 events (in 19 patients) occurred in patients with sJIA and 2 events (in 2 patients) occurred in patients with adult onset Still's disease (AOSD). The 2 events (in 2 patients) that occurred in patients with AOSD were assessed as definite MAS and insufficient data to make a decision.

The incidence of MAS observed in WA18221, Chugai sJIA studies, and Chugai postmarketing surveillance (JPMS) studies was 2.7%, 2.7%, and 3.8%, respectively. These incidence calculations compared favorably with the estimated background incidence of MAS between 6.8% and 8.2% in sJIA patients (Sawhney et al., 2001). Thus, the data does not support an association between the use of TCZ and an increased risk of developing MAS in patients with sJIA.

Table 21. WA18221 Safety Population Summary of CTC Grade Neutropenia

Summary of Worst CTC Grades for Neutrophils: Week 12 versus May 2010 data cutoff (WA18221 Safety Population)					
Neutrophils	PBO N=37	TCZ 8 mg/kg N=37	TCZ 12 mg/kg N=38	TCZ ALL Wk 12 N=75	TCZ May 2010 N=112
	No./%	No./%	No./%	No./%	No./%
Normal	35(100)	30(81)	29(76)	59(79)	59(53)
GRADE-1	0(0)	0(0)	0(0)	0(0)	5(5)
GRADE-2	0(0)	4(11)	6(16)	10(13)	31(28)
GRADE-3	0(0)	2(5)	3(8)	5(7)	15(13)
GRADE-4	0(0)	1(3)	0(0)	1(3)	2(2)

Summary of Clinical Safety Tables 36 and 37.

The WA18221 safety population summary of CTC Grade neutrophilia is shown in Table 21 above. The incidence of Grace-2 to -4 neutropenia was comparable across TCZ subgroups. As of the May 2010 data cutoff, 28% of subjects experienced Grade-2 neutropenia; 13% had Grade-3 neutropenia, and 2% had Grade-4 neutropenia.

In the Chugai all exposure population (149 patients), the neutrophil count remained in the normal range during study treatment in 82 patients (55%). Twenty nine (20%) and 18 patients (12%) experienced grade 1 and grade 2 neutropenia, respectively. Of the 20 patients (13%) who experienced grade 3 (16 patients; 11%) or grade 4 neutropenia (4 patients; 3%), the decrease in neutrophil count was transient in 11 patients. In the other 9 patients who had non-transient decreases in neutrophil count to at least grade 3 abnormality, 1 had EBV infection, 1 developed MAS at the time of neutropenia, and the other 7 reported AEs that were categorized as Infections and Infestations.

Table 22. Study WA18221 Wk 12 Summary of Infection AE by Neutrophil Counts

Summary of Total Number of Infection Adverse Events by Neutrophil Counts (12 Week Results, Study WA18221, Safety Population)					
Treatment	500 x 10^6/L n(%)	500-1000 x 10^6/L n(%)	1000- x 10^6/L n(%)	>/= LLN	Missing
PBO (n=37)	0	0	0	14(93)	1(7)
TCZ 8 mg/kg (n=37)	0	0	0	21(100)	0
TCZ 12 mg/kg (n=38)	0	2(5)	0	36(92)	1(3)
All TCZ (n=75)	0	2(3)	0	57(95)	1(2)

Source: Summary of Clinical Safety, Table 26.

Table 22 depicts Week 12 summary of infection AE by neutrophil counts. Only two events of infection, both in the TCZ 12 mg/kg group, occurred at neutrophil counts below the lower level of normal.

Liver Function Test Abnormalities

Table 23. Summary of Worst CTC Grades for ALT, AST and Bilirubin: Week 12 versus May 2010 Data Cut

Summary of Worst CTC Grades for ALT, AST and Bilirubin: Week 12 vs May 2010 Data Cut					
	PBO (N=35)	TCZ 8 mg/kg	TCZ 12 mg/kg	TCZ ALL (N=75)	May 2010 TCZ ALL (N=112)
ALT (SGPT)					
Normal	32(91%)	24(65%)	29(76%)	53(71%)	58(52%)
Grade 1	3 (9%)	8(22%)	8(21%)	16(21%)	36(32%)
Grade 2	0	4(11%)	1(3%)	5(7%)	10(9%)
Grade 3	0	1(3%)	0	1(1%)	8(7%)
AST (SGOT)					
Normal	35(100%)	24(65%)	37(97%)	61(81%)	67(60%)
Grade 1	0	11(30%)	1(3%)	12(16%)	39(35%)
Grade 2	0	2(5%)	0	2(3%)	4(4%)
Grade 3	0	2(5%)	0	2(3%)	1(1%)
Grade 4	0	0	0	0	1(1%)
Total Bilirubin					
Normal	35(100%)	35(95%)	37(97%)	72(96%)	96(86%)
Grade 1	0	1(3%)	1(3%)	2(3%)	11(10%)
Grade 2	0	1(3%)	0	1(1%)	5(5%)

Percentages are based on n.
At post-Baseline visits only worst values within a time window per patient are summarized.
Overall does not include Baseline.
Baseline considered to be first dose of TCZ treatment.
Local analysis is excluded where central analysis is available on the same day.
CTC Grades Version 3.0.
The mutually exclusive CTC grades are NORMAL, GRADE 1, GRADE 2, GRADE 3 and GRADE 4.
Data on Placebo treatment from study part I is excluded.
Source: Adapted from Summary of Clinical Safety, Tables 42-45.

Worst CTC grades for ALT, AST and bilirubin are summarized in Table 23 above, by data at Week 12 versus the May 2010 cutoff. ALT values remained in the normal range during the 12 weeks of conrolled study treatment in 71% of patients treated with TCZ compared with 91% in those treated with PBO. With TCZ treatment, 21% and 67% of patients had grade 1 and grade 2 elevations of ALT values, respectively, compared with 9% and 0% in PBO-treated patients. Of the 4 TCZ-treated patients with an ALT value ≥ 3 × ULN during 12 weeks of study treatment (3 with TCZ 8 mg/kg and 1 with TCZ 12 mg/kg), 1 had an ALT consecutive elevation, 1 had an ALT sustained elevation, 1 had an ALT non-consecutive elevation, and 1 had an ALT elevation at a single time point. None of the patients with an ALT value ≥ 3 × ULN had simultaneous total bilirubin ≥ 2 × ULN.

During study treatment to Week 12, AST values remained in the normal range in 81% of patients treated with TCZ compared with 100% in patients treated with PBO. Grade 1 and grade 2 elevation of AST were observed in 16% and 3% of patients treated with TCZ, respectively

(Table 1). These AST abnormalities were predominantly seen in patients receiving TCZ 8 mg/kg. The only AST abnormality seen in TCZ 12 mg/kg (1 patient, 3%) was a grade 1 AST elevation. No AST abnormalities were observed in placebo-treated patients.

Two patients in the TCZ 8 mg/kg group experienced an AST elevation to ≥ 3 × ULN. Of these 2 cases, 1 was an AST consecutive elevation, and the other a single elevation. None of the patients with an AST value ≥ 3 × ULN had concurrent total bilirubin > 2 × ULN.

Autoimmune Disorders

Autoimmune disorders have been reported in RA patients receiving TCZ treatment. The most common autoimmune disorders were psoriasis, vasculitis, Sjögren's syndrome, sicca syndrome, and autoimmune thyroiditis. There was 1 patient with systemic lupus, 2 patients with a lupus-like syndrome, and 3 patients with cutaneous lupus. Four patients were reported with Crohn's disease and 1 patient was reported with autoimmune hepatitis. Overall, the observed type and incidence of autoimmune disorders were within the expected range for a population of patients with RA.

To date, no autoimmune disorders have been reported in sJIA patients treated with TCZ.

Potential Demyelinating Disorders

As of the clinical cut off of February 17, 2010, there has been a total of 3 potential Demyelinating Disorder cases that have been identified in the all exposure population in RA patients. Upon review, none of these cases were considered to represent cases of new onset demyelination. Follow-ups of these patients continue.

In regards to the cases from the sJIA population, as of the May 2010 clinical data cutoff date, there was 1 event in the Roche TCZ compassionate use program for sJIA that could potentially be identified as suggestive of a demyelination event. This case occurred in a 13 year-old male patient (MCN 661417) who developed a benign tic disorder and the MRI showed non specific punctuate hyper-intensities.

No potential Demyelinating Disorder events have been reported in study WA18221.

Lipid Abnormalities

Table 24. Study WA18221 Summary of Lipid Abnormalities

Study WA18221 Summary of Lipid Abnormalities to Week 12				
	PBO N=37	TCZ 8 mg/kg N=37	TCZ 12 mg/kg N=38	TCZ ALL Wk 12 N=75
Total Cholesterol				
Baseline				
Normal	32(94%)	31(94%)	33(97%)	64(96%)
>ULN-1.5 x ULN	2(6%)	2(6%)	1(3%)	3(5%)
>1.5-2 x ULN	0	0	0	0
Week 2				
Normal	32(94%)	23(70%)	23(66%)	46(68%)
>ULN-1.5 x ULN	2(4%)	9(27%)	12(34%)	21(31%)
>1.5-2 x ULN	0	0	0	1(1%)
Week 12				
Normal	14(88%)	28(85%	29(85%)	57(85%)
>ULN-1.5 x ULN	2(12%)	5(15%)	5(15%)	10(15%)
>1.5-2 x ULN	0	0	0	0
LDL Cholesterol				
Baseline				
Normal	17(94%)	20(91%)	16(100%)	36(95%)
>ULN-1.5 x ULN	1(6%)	2(9%)	0	2(5%)
>1.5-2 x ULN	0	0	0	0
Week 2				
Normal	30(97%)	26(37%)	27(93%)	53(90%)
>ULN-1.5 x ULN	1(3%)	3(10%)	2(7%)	5(9%)
>1.5-2 x ULN	0	1(3%)	0	1(2%)
Week 12				
Normal	13(93%)	24(96%)	25(93%)	49(94%)
>ULN-1.5 x ULN	1(7%)	0	2(7%)	2(4%)
>1.5-2 x ULN	0	1(4%)	0	1(2%)
HDL Cholesterol				
Baseline				
Normal	18(100%)	20(91%)	16(100%)	36(95%)
>ULN-1.5 x ULN	0	2(9%)	0	2(5%)
Week 2				
Normal	31(100%)	28(93%)	26(90%)	54(92%)
>ULN-1.5 x ULN	0	2(7%)	3(10%)	5(9%)
Week 12				
Normal	14(100%)	22(85%)	26(96%)	48(91%)
>ULN-1.5 x ULN	0	4(15%)	1(4%)	5(9%)

Source: Summary of Clinical Safety, Table 46.

Table 24 depicts the summary of lipid abnormalities in study WA18221 to Week 12. Lipid parameters that were assessed (in the fasted state) included total cholesterol, LDL-cholesterol, and HDL-cholesterol.

At Baseline, a small proportion of patients (5% with TCZ and 6% with placebo) had a total cholesterol value of > ULN to 1.5 × ULN. At Week 2, 31% of patients receiving TCZ had a total cholesterol value in this category, which reduced to 15% at Week 12. One additional patient receiving TCZ 8 mg/kg experienced a total cholesterol value > 1.5 to 2 × ULN at Week 2 but not at Week 12. The number of patients with an abnormal total cholesterol in the placebo group (2 patients) did not change during study treatment.

The pattern of LDL-cholesterol abnormalities during study treatment was similar to that of total cholesterol, but the proportion of TCZ-treated patients experiencing an elevated

LDL-cholesterol value to > ULN to 1.5 × ULN at both Weeks 2 and 12 was lower, 5% at Baseline, 9% at Week 2, and 4% at Week 12. In addition, 1 patient (1002) with TCZ 8 mg/kg had an LDL-cholesterol value > 1.5 to 2 × ULN at both Weeks 2 and 12. Of note, patient 1002 had a baseline LDL-cholesterol value > ULN at Baseline.

The percentage of TCZ-treated patients with HDL-cholesterol elevations increased during study treatment, 5% at Baseline, 9% at Week 2, and 9% at Week 12. In the TCZ 8 mg/kg group, the percentage of patients with HDL-cholesterol abnormalities increased from 7% at Week 2 to 15% at Week 12. All the HDL-cholesterol abnormalities was within 1.5 × ULN category, and no patient had an HDL-cholesterol abnormality > 1.5 × ULN category.

Gastrointestinal (GI) Perforations

As of February 2010, GI perforation was reported in 29 patients receiving TCZ in Roche RA studies; this is equivalent to a rate 2.36 per 1000 patient-years of exposure (0.236 per 100 patient-years). In 17 of 19 patients (89%) with colon perforations, the underlying pathology was diverticulitis. Patient age ranged from 51 to 82 years (mean of 63 years) at study initiation.

No GI perforations were reported in study WA18221. One GI perforation was reported in the Chugai supportive studies (study MRA011JP), duodenal perforation was observed in one patient, a 10 year old male with sJIA. Prior to TCZ treatment he had been on CS and NSAID therapy and had suffered epigastralgia and gastrointestinal hemorrhage. The patient responded to TCZ and tapered off corticosteroids over 6 months. During the course of TCZ treatment, famotidine/lansoprazole was repeatedly started and discontinued. On study Day 304, 12 days after TCZ treatment and discontinuation of lansoprazole, he developed epigastralgia again, was admitted to the hospital and diagnosed as having a duodenal perforation. The event was resolved after surgery. The patient was withdrawn from study MRA011JP but continued TCZ treatment under the compassionate use program. Although pre-existing gastrointestinal disorders, previous CS and NSAID treatment and intermittent use of proton-pump inhibitors were likely contributors to the duodenal perforation, causal relationship with TCZ cannot be excluded.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 25. WA18221 Summary of AE ≥ 5% by Preferred Term and Treatment, 12 Week Data versus May 10, 2010 Data Cut (Safety Population)

WA18221 12 Week Data versus May 10, 2010 Data:Summary of AE with an Incidence Rate of >/= 5% by Preferred Term and Treatment					
Adverse Event	PBO N=37 No. (%)	TCZ 8 mg/kg N= 37 No. (%)	TCZ 12 mg/kg N= 38 No. (%)	ALL TCZ 12 Wk N=75 No. (%)	TCZ ALL N=112 No. (%)
Upper Respiratory Infection	4(11)	4(11)	6(16)	10(13)	32(29)
Headache	3(8)	5(14)	2(5)	7(9)	17(15)
Nasopharyngitis	1(3)	2(5)	6(16)	8(11)	33(30)
Diarrhea	1(3)	3(8)	2(5)	5(7)	17(15)
Juvenile Arthritis	5(24)	0	2(5)	2(3)	27(24)
Neutropenia	1(3)	1(3)	2(5)	3(4)	16(14)
Oropharyngeal Pain	1(3)	2(5)	1(3)	3(4)	11(10)
Arthropod Bite	0	1(3)	2(5)	3(4)	11(10)
Back Pain	0	1(3)	2(5)	3(4)	8(7)
Viral Gastroenteritis	0	1(3)	2(5)	3(4)	10(9)
Pharyngitis	2(5)	1(3)	1(3)	2(3)	6(5)
Pyrexia	6(16)	0	0	0	5(5)
Urticaria	0	0	3(8)	3(4)	7(6)
Vomiting	0	2(5)	1(3)	3(4)	13(11)
Cough	1(3)	2(5)	0	2(5)	20(18)
Dizziness	1(3)	2(5)	0	2(5)	11(10)
Hematuria	1(3)	0	2(5)	2(5)	3(3)
Abdominal Pain	0	0	2(5)	2(5)	8(7)
Dysmenorrhoea	0	2(5)	0	2(5)	3(3)
Gastrointestinal D/O	0	2(5)	0	2(5)	5(5)
Flu-like Illness	2(5)	1(3)	0	1(3)	9(8)
Joint Sprain	0	2(5)	0	1(3)	6(5)

Source: Summary of Clinical Safety, Table 15.

In the Chugai all exposure population, the AE system organ classes that reported AEs most frequently were Infections and Infestations (91%), Skin and Subcutaneous Disorders (67%), Investigations (59%), Gastrointestinal Disorders (57%), Injury, Poisoning, and Procedural Complications (49%), Respiratory, Thoracic, and Mediastinal Disorders (35%), Eye Disorders (32%), and Musculoskeletal and Connective Tissue Disorder (23%). This order was similar to that observed for the long-term extension data in study WA18221.

In the system organ class of Infections and Infestations, the most frequent infection AEs were those involving upper respiratory tract including nasopharyngitis (59%), upper respiratory tract infection (46%), and pharyngitis (34%). Gastroenteritis (40%) and bronchitis or bronchitis acute (all together 25%) were also frequent infection AEs.

Eczema (29%), urticaria (17%), and ingrowing nail (11%) were the most frequently reported AEs in the system organ class of Skin and Subcutaneous Disorders. The system organ class of Investigations was largely composed of laboratory abnormalities; the most frequent were ALT increased (22%), AST increased (17%), LDH increase (17%), lymphocyte count decreased (17%), hypercholesteremia (12%), and neutropenia (12%).

The most common AEs in the system organ class of Gastrointestinal Disorders were diarrhea (19%), vomiting (12%), stomatitis (11%), and nausea (7%).

The most common AEs in the system organ class of Injury, Poisoning, and Procedural Complications were arthropod sting (24%) and contusion (10%).

Thirty-two cases of upper respiratory tract infection (22%) were reported under the system organ class of Respiratory Disorders; the most common AE under this system organ class. Allergic rhinitis was reported in 7% of patients.

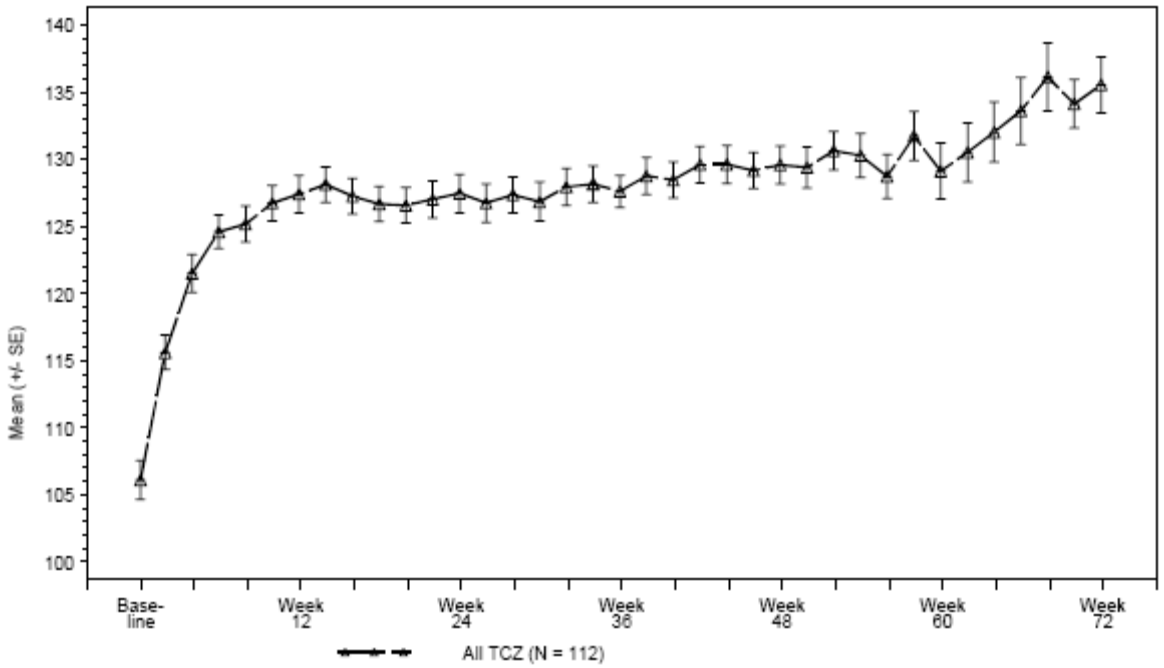
Conjunctivitis (7%) was the most frequent Eye Disorder. In addition, allergic conjunctivitis was reported in 3% of patients.

7.4.2 Laboratory Findings

Hemoglobin

Mean hemoglobin (Hgb) concentrations increased from Baseline values at Week 2 and continued to increase during the controlled 12 weeks of treatment in TCZ-treated patients. This was observed in all age subgroups receiving TCZ and also in patients with a Baseline Hgb level below the LLN. In patients whose Baseline Hgb levels were higher than the LLN, those receiving TCZ had an increase in mean Hgb whereas those receiving placebo had a decrease in mean Hgb during 12 weeks of treatment. The Hgb level was also assessed by assessing each patient's lowest Hgb value to Week 12 according to the CTC grade (normal, 1, 2, 3, or 4). In 43% of the patients treated with TCZ, the lowest Hgb value remained within the normal range during 12 weeks of treatment, compared with 17% of patients treated with placebo.

Figure 4. Line Plot of Mean Hgb (Untransformed Values) to Week 72 (Study WA18221, Safety Population)



Only worst values within a time window per patient are summarised. Local analysis is excluded where central analysis is available on the same day.
Baseline considered to be first dose of TCZ treatment.
SE = Standard Error.

Program : $PROD/cs11935b/b18221b/sglbsmnp01.sas
Output : $PROD/cs11935b/b18221b/reports/sglbsmnp01_hgbu_visu_2_rx1.cgm
23JUL2010 17:23

Source: Summary of Clinical Safety, Figure 2, p 133.

Data to the May 2010 data cutoff indicate that mean Hgb concentrations at Baseline were below the LLN in all age subgroups, and increased to within the normal range in all age subgroups during study treatment with TCZ. Overall, 35% of patients in the all TCZ group had normal Hgb throughout study treatment, 46% and 16% of patients had a CTC grade 1 and 2 Hgb value, respectively, and 2% and 1% of patients had a CTC grade 3 and 4 Hgb value, respectively. See Figure 1 above for a plot of mean Hgb up to Week 72 for the all TCZ group.

In the Chugai all exposure population, compared with the Baseline value, mean Hgb concentrations increased slightly but steadily throughout the TCZ treatment period. The Hgb level was also assessed by assessing each patient's lowest Hgb value during study treatment according to the CTC grade (normal, 1, 2, 3, or 4). Of the 149 patients in the all exposure population, the lowest Hgb value remained normal in 43 patients (29%). The worst CTC grade of 1, 2, 3, and 4 was observed in 72 (48%), 25 (17%), 8 (5%), and 1 patient (1%), respectively.

Lymphocytes

Table 26. Worst CTC Grades of Lymphocyte Count (WA18221 Safety Population)

Summary of Worst CTC Grades of Lymphocyte Counts (Hypo-) byTrial Treatment- May 10, 2010 Data Cut (Study WA18221 Safety Population)					
Lymphocytes Overall	TCZ 8 mg/kg No./%	TCZ 12 mg/kg No./%	TCZ 8 to 12 mg/kg No./%	TCZ 12 to 8 mg/kg No./%	TCZ ALL N=112 No./%
N	52	50	1	9	112
Grade-1	38(73%)	35(70%)	1(100%)	6(67%)	80(71%)
Grade-2	8(15%)	11(22%)	0(0%)	2(22%)	21(19%)
Grade-3	5(9%)	4(8%)	0(0%)	1(11%)	10(9%)
Grade-4	1(2%)	0(0%)	0(0%)	0(0%)	1(1%)

Percentages are based on n.
At post-Baseline visits only worst values within a time window per patient are summarized.
Overall does not include Baseline.
Baseline considered to be first dose of TCZ treatment.
Local analysis is excluded where central analysis is available on the same day.
CTC Grades Version 3.0.
The mutually exclusive CTC grades are NORMAL, GRADE -1, GRADE -2, GRADE -3 and GRADE -4.
Source: Summary of Clinical Safety, Table 39.

In study WA18221, mean lymphocyte counts were within the normal range and stable during study treatment to Week 12 in both the placebo- and TCZ-treated patients of all age subgroups. As summarized in Table 26, throughout study treatment to May 10, 2010 data cut, 71% of patients in the all TCZ group had a normal lymphocyte count, and 19% and 9% of patients showed a CTC grade 1 and 2 lymphocytopenia, respectively. In addition, 1 patient had a CTC grade 3 lymphocytopenia.

In the Chugai sJIA studies, mean lymphocyte counts were stable and did not change markedly throughout study treatment period (to 192 weeks). In the all exposure population (149 patients), the lymphocyte count remained in the normal range during study treatment in 36 patients (24%). Thirty five (24%) and 58 patients (39%) experienced grade 1 and grade 2 lymphocytopenia, respectively. A total of 20 patients (13%) experienced grade 3 lymphocytopenia, and no patients reported grade 4 lymphocytopenia during study treatment.

Thrombocytopenia

In study WA18221, during study treatment, the lowest platelet count remained normal in 77% of patients, with 22% of patients experiencing CTC grade 1 thrombocytopenia and 1 patient (1%) having CTC grade 3 thrombocytopenia. The only case with a platelet depression to CTC grade 3 was a single time point depression. No CTC grade 2 or 4 thrombocytopenia was observed. Decreased platelet count to $\leq 100 \times 109/L$ occurred in 3% of patients treated with TCZ.

In the all exposure population, mean platelet count decreased by approximately 25% to 35% from Baseline and remained stable during study treatment period. During study treatment, the worst platelet count was grade 1 thrombocytopenia in 21 patients (14%) and grade 2 thrombocytopenia in 2 patients (1%). None had a grade 3 or 4 thrombocytopenia.

7.4.3 Vital Signs

Table 27. Table Summary of Abnormal Vital Signs by Trial Treatment (WA18221 Safety Population)

Summary of Abnormal Vital Signs by Trial Treatment, May 10, 2010 Data Cut (WA18221, Safety Population)					
Adverse Event	TCZ 8 mg/kg No./%	TCZ 12 mg/kg No./%	TCZ 8 to 12 mg/kg No./%	TCZ 12 to 8 mg/kg No./%	TCZ ALL No./%
SBP - High (>ULN and Increased >20 CFB)					
NO	34 (65%)	26 (52%)	1	5	66 (59%)
YES	18 (35%)	24 (48%)	0	4	46 (41%)
n	52	50	1	9	112
SBP - Low (<LLN and Decreased >20 CFB)					
NO	20 (38%)	16 (32%)	0	6	42 (38%)
YES	32 (62%)	34 (68%)	1	3	70 (63%)
n	52	50	1	9	112
DBP - High (>ULN and Increased >20 CFB)					
NO	32 (62%)	24 (48%)	1	7	64 (57%)
YES	20 (38%)	26 (52%)	0	2	48 (43%)
n	52	50	1	9	112
DBP - Low (<LLN and Decreased >20 CFB)					
NO	33 (63%)	29 (58%)	0	5	67 (60%)
YES	19 (37%)	21 (42%)	1	4	45 (40%)
n	52	50	1	9	112
Heart Rate -High (>ULN and Increased >20CFB)					
NO	34 (65%)	32 (64%)	1	7	74 (66%)
YES	18 (35%)	18 (36%)	0	2	38 (34%)
n	52	50	1	9	112
Heart Rate -Low (<LLN and Decreased >20 CFB)					
NO	31 (60%)	21 (42%)	1	3	56 (50%)
YES	21 (40%)	29 (58%)	0	6	56 (50%)
n	52	50	1	9	112
Weight - High (Increased >10% CFB)					
NO	22 (42%)	15 (30%)	1	0	38 (34%)
YES	30 (58%)	35 (70%)	0	9	74 (66%)
n	52	50	1	9	112
Weight - Low (Decreased >10% CFB)					
NO	51 (98%)	48 (96%)	0	9	108 (96%)
YES	1 (2%)	2(4%)	1	0	1
n	52	50	1	9	112

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DBP Semi-Supine (mmHg): age 2-5 (LLN=65, ULN=75), age 6-12 (LLN=70, ULN=80), age 13-18 (LLN=75, ULN=85).
SBP Semi-Supine (mmHg): age 2-5 (LLN=100, ULN=115), age 6-12 (LLN=110, ULN=125), age 13-18 (LLN=120, ULN=135).
Heart Rate (beats/min): age 2-5 (LLN=80, ULN=130), age 6-12 (LLN=70, ULN=115), age 13-18 (LLN=60, ULN=100).
LLN = Lower Limit of Normal. ULN = Upper Limit of Normal. CFB = Change from Baseline.
Baseline considered to be first dose of TCZ treatment.
Source: Summary of Clinical Safety pages 10039-10040.

In the May 10, 2010 data cut of the WA19221 long-term extension vital signs were relatively stable, but vital sign parameters out of the normal range were recorded at one or more occasions

during study treatment in a portion of patients. However, as summarized in Table 27 above, there were ≥ 10% differences in the percentage of patients with high and low heart rates and weight gain between the TCZ group and the placebo group. High heart rate (>ULN and increased >20 beats per minute (bpm) from Baseline) was reported by fewer patients in the TCZ group (15%) compared to the placebo group (31%) whereas low heart rate (<LLN and decreased >20 bpm from Baseline) was reported by more patients in the TCZ group (15%) compared with the placebo group (3%). These differences do not appear to be clinically significant. In addition, the Sponsor reports that in evaluating the changes in blood pressure by history of hypertension, it was found that the number and percentage of patients with low systolic and high diastolic blood pressures in the two TCZ treatment groups remained fairly constant in those patients with a history and those without a history of hypertension.

The body weight measurements in the long term extension population to date (Table 27) showed that in the all TCZ group, 66% of patients had a gain of body weight by more than 10% during study treatment (58% in the TCZ 8 mg/kg group and 70% in the TCZ 12 mg/kg group). The weight gain may be reflective of improved disease control, as complications of sJIA include malnutrition, growth retardation, and other growth disturbances. Four patients (4%) had a > 10% loss in body weight during study treatment, 1 in the TCZ 8 mg/kg group, 2 in the TCZ 12 mg/kg group, and an additional patient with the TCZ dose shifting from 8 to 12 mg/kg.

Vital sign data provided for the Chugai supportive studies are derived from studies MRA317JP/MRA/324JP and comprise baseline to Week 336 (data from 52% of patients are available to week 168). The time course indicated that mean body temperature tended to decrease towards normal at 12 weeks after the start of study treatment, and remained stable thereafter. Mean pulse rate and SBP tended to decrease after the start of study treatment as well. No marked variations in the time course of mean DBP were observed.

7.4.4 Electrocardiograms (ECGs)

Because of cardiac conduction abnormalities observed in a Castleman's Disease clinical
trial, the approved Japanese label for TCZ contains a precaution about cardiac abnormalities and a recommendation that ECG testing should be conducted periodically.
Therapeutic biologics, such as TCZ, are macromolecules with specific targets that
are not considered likely to be able to affect the cardiac conduction system. In order to further examine this issue, the applicant has conducted a 2-part QT study,
BP19461. This study was a single-center, randomized double-blind, placebo-controlled
(6:2, active:placebo) study in 36 healthy volunteers who were given a single dose of TCZ

at 2, 10, 20, or 28 mg/kg IV vs. placebo. ECG recordings were taken at baseline, then 2 hours after the start of infusion and weekly thereafter until Day 29. An ECG was also performed at the final follow-up visit on Day 50. All mean QTc values were <450 ms within 28 days for all subjects, except for the day 8 (QTcF 455 ms) and day 29 (QTcF 454 ms) values for one female subject who had received TCZ 20 mg/kg. No significant change from baseline in QTc were noted with the exception of a single male who had received placebo and had a change in QTcF of 32 ms on day 15. The final study report for the 2nd part of the study, which includes a more thorough QT evaluation of single doses of 10 mg/kg and 20 mg/kg, is pending review.

For pivotal study WA18221, Twelve lead ECGs with formal readings were taken at screening only. Two consecutive ECGs were done two to five minutes apart and results of each recorded in the eCRF. An ECG could be performed at any time for safety reasons as required in the appropriate evaluation of an AE and the results included in the description of the AE.

7.4.5 Special Safety Studies

No additional safety studies were performed for this application.

7.4.6 Immunogenicity

Immunogenicity was not tested in the sJIA Chugai supportive studies; thus available data are from study WA18221. In study WA18221, all patients (N=112) were tested at baseline and Week 12 for anti-TCZ antibodies. All patients with assay results were negative at baseline for both confirmative and neutralizing assays. Only two patients (1664 and 1005) with assay results were positive for both confirmation assay as well as neutralizing assay at Week 12. The small number of positive results should be interpreted in light of the relatively small database of TCZ-treated patients (N=72).

Both patient 1664 and 1005 withdrew at or immediately after the Week 8 infusion due to SAEs. Patient 1664, had an anaphylactic reaction of life-threatening angioedema during the Week 8 infusion. This event was preceded by a SAE of urticaria directly after the Week 4 infusion, which required treatment with iv corticosteroids. The other patient, 1005, had an event of MAS

diagnosed a (b) (6) after the Week 8 infusion. This event was preceded by partial infusions at Weeks 4 and 6 due to a constellation of infusion reaction-like symptoms such as back pain, shortness of breath, and changes in blood pressure, which were managed by stopping the infusion and, in one case, receiving paracetamol.

No patient who missed consecutive infusions tested positive for anti-TCZ antibodies after restarting dosing. Four patients, two from the TCZ 8 mg/kg group and 2 from the TCZ 12 mg/kg group, prematurely discontinued study treatment for lack of efficacy. None of these patients had a positive anti-TCZ-neutralizing assay.

In the Chugai studies, patients were withdrawn from study treatment if anti-TCZ antibodies were confirmed, independent of patients' efficacy response and tolerability data. Seven patients (5%) who participated in the Chugai sJIA studies were withdrawn because of the appearance of anti-TCZ antibodies

Infusion Reactions

Table 28. AE Occurring Within 24 hours of Infusion (WA18221 Safety Population)

Summary of AE Occurring Within 24 hours of Infusion by Body System, Preferred Term and Trial Treatment- May 10, 2010 Data Cut (WA18221 Safety Population)					
BodySystem/AE	TCZ 8 mg/kg N=52 No(%)	TCZ 12 mg/kg N=50 No(%)	TCZ 8-12 mg/kg N=1 No(%)	TCZ 12 mg/kg N=9 No(%)	ALL TCZ N=52 No(%)
ALL BODY SYSTEMS					
Total at Least one AE	16(31)	17(34)	0	4	37(33)
Total Number AE	31	34	0	4	69
INFECTIONS/INFEST					
Total at Least one AE	6(12)	8(16)	0	2	16(14)
Nasopharyngitis	1(2)	1(2)	0	1	3(3)
URI	2(4)	1(2)	0	0	3(3)
Ear Infection	0	2(4)	0	0	2(2)
GASTROINTEST D/O					
Total at Least one AE	5(10)	7(14)	0	0	12(11)
Diarrhea	3(6)	4(8)	0	0	7(6)
Vomiting	0	2(4)	0	0	2(2)
SKIN and SQ D/O					
Total at Least one AE	4(8)	3(6)	0	0	7(6)
Urticaria	1(2)	2(4)	0	0	3(3)
Rash	2(4)	0	0	0	1(1)
MSKEL D/O					
Total at Least one AE	1(2)	4(8)	0	1	6(5)
Juvenile Arthritis	0	3(6)	0	0	3(3)
NERVOUS SYST D/O					
Total at Least one AE	3(6)	2(4)	0	0	5(5)
Headache	2(4)	2(4)	0	0	4(4)
RESP/THORACIC/ MEDIASTINAL D/O					
Total at Least one AE	2(4)	2(4)	0	0	4(4)
Cough	0	2(4)	0	0	2(2)
GENL D/O					
Total at Least one AE	1(2)	2(4)	0	0	3(3)
Peripheral Edema	1(2)	1(2)	0	0	2(2)
Infusion Related Rx			0	0	1(1)
IMMUNE SYST D/O					
Total at Least one AE	1(2)	0	0	0	1(2)
Drug Hypersensitivity	1(2)	0	0	0	1(2)

Source: Summary of Clinical Safety, Table 32.

Table 28 provides a summary of AEs that occurred within 24 hours following infusion. A total of 37 patients (33%) in the all TCZ group reported 69 such events, with an AE rate of 56 per 100 patient-years. The incidence of AEs occurring within 24 hours after infusion was similar in the two TCZ dosing groups. The system organ classes with the most frequent AEs reported within 24 hours following infusion were Infections and Infestations (14%), Gastrointestinal Disorders (11%), and Skin and subcutaneous Tissue Disorders (6%). There was 1 SAE, urticaria, occurring within 24 hours of infusion in patient 1664 with TCZ 12 mg/kg treatment. The

majority of patients reporting AEs within 24 hours after infusion were given treatment, and all the events resolved without sequelae.

Table 29. AE Occurring During Infusion (WA18221 Safety Population)

Summary of AE Occurring During Infusion by Body System, Preferred Term and Trial Treatment- Data to Week 12 (WA18221 Safety Population)					
BodySystem/AE	TCZ 8 mg/kg N=52 No(%)	TCZ 12 mg/kg N=50 No(%)	TCZ 8-12 mg/kg N=1 No(%)	TCZ 12 mg/kg N=9 No(%)	ALL TCZ N=52 No(%)
ALL BODY SYSTEMS					
Total at Least one AE	2(4)	6(12)	0	1	9(8)
Total Number AE	3	3(6)	0	1	11
GENERAL D/O					
Total at Least one AE	1(2)	4(8)	0	1	6(5)
Infusion related rx	0	3(6)	0	0	3(3)
Asthenia	1(2)	0	0	0	1(1)
Catheter site erythema	0	1(2)	0	0	1(1)
Puncture site pain	0	0	0	1	1(1)
Total Number AE	1	4	0	1	6
SKIN and SQ D/O					
Total at least one AE	0	2(4)	0	0	2(2)
Angioedema	0	1(2)	0	0	1(1)
Rash	0	1(2)	0	0	1(1)
Total Number AE	0	2	0	0	2
GASTROINTESTINAL D/O					
Total at least one AE	0	1(2)	0	0	1(1)
Vomiting	0	1(2)	0	0	1(1)
Total Number AE	0	1	0	0	1
MSKEL and CT D/O					
Total at least one AE	1(2)	0	0	0	1(1)
Vomiting	1(2)	0	0	0	1(1)
Total Number AE	1	0	0	0	1
NERVOUS SYSTEM D/O					
Total at least one AE	1(2)	0	0	0	1(1)
Somnolence	1(2)	0	0	0	1(1)
Total Number AE	1	0	0	0	1

Source: Summary of Clinical Safety, Table 31.

In the all TCZ group, 11 AEs occurring during infusion were reported in 9 patients (8%), including 3 events in 2 patients (4%) in the TCZ 8 mg/kg group, 7 events in 6 patients (12%) in the TCZ 12 mg/kg, and 1 event in a patient who switched from receiving TCZ 12 mg/kg to 8 mg/kg (Table 29). The rate of AEs occurring during infusion was 9.8 per 100 patient-years in the all TCZ group. All these events occurred in a single patient except for infusion related reaction, which was observed in 3 patients. One of the 3 patients (patient 1005) who reported infusion related reaction twice (Days 17 and 29 and both considered severe AEs) had her TCZ dose interrupted twice and later withdrew from study treatment for a MAS event. The event in patient 1664 was considered a lifethreatening event of angioedema and led to discontinuation of the study drug. Five of the 9 patients having AEs during infusion received treatment, and all the events resolved without sequelae.

In the Chugai all exposure population, 24 patients (16%) reported 45 infusion reactions (AE

within 24 hours after TCZ administration). The infusion reaction event terms reported included chills (5%), pyrexia (4%), vomiting and headache (3% each), nausea, pruritus and infusion related reaction (2% each), rhinitis, anaphylactoid reaction, flushing, and exanthema (1% each), and dizziness, drug eruption, chest pain, malaise, and blood pressure decreased (0.7% each).

Sampson's Criteria

Although safety data was submitted regarding infusion reactions occurring during infusion and within 24 hour of infusion (Table 28 & Table 29 above), the Agency is primarily concerned with the incidence of anaphylaxis by Sampson's criteria associated with infusions. The TCZ pediatric sJIA data were searched for events that met the clinical criteria for diagnosing anaphylaxis, as defined in the statement paper from the Second Symposium on the Definition and Management of Anaphylaxis: (Sampson et al., 2006)

It is reasoned that anaphylaxis is highly likely when any one of three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both; and at least one of the following:
    a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): involvement of the skin-mucosal tissue, respiratory compromise, reduced BP or associated symptoms or persistent gastrointestinal symptoms; and
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours).

The Applicant conducted Sampson Criteria 1 and 2 search strategies of WA18221 data to the May 10, 2010 data cut. Criterion 3 was not deemed applicable as TCZ is not a 'known allergen' for study participants. Pediatric patients with sJIA were not eligible to participate in TCZ clinical trials if they had a history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. In addition, patients who experienced a severe hypersensitivity reaction attributed to the infusion in the clinical trial discontinued treatment and were removed from the clinical trial. Due to these safety provisions in the TCZ clinical trial program, no patient with a known allergy to TCZ should have been dosed with TCZ.

The search reportedly identified 3 patients who potentially satisfied Sampson's criteria 1 or 2. Two of these patients (1664 and 1131) met the criteria for diagnosing anaphylaxis set forth in the statement paper from the Second Symposium on the Definition and Management of Anaphylaxis (Sampson et al., 2006). Upon medical review, patient 1664 had clinically apparent hypersensitivity and therefore, discontinued TCZ. The other patient (1131) did not have a clinically apparent anaphylactic reaction and tolerated continued therapy without clinical symptoms of anaphylaxis. A third patient identified by the search strategy (1121) did not meet Sampson's criterion 2 as a result of the patient having occasional abdominal pain prior to TCZ infusion and because the event of hypotension was thought to be related to the patient's

antihypertensive medications. Therefore, 1 patient (1664) met the criteria of anaphylaxis (< 1.0%).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Sections 7.3 and 7.4 above present AE data according to dose administered.

7.5.2 Time Dependency for Adverse Events

Sections 7.3 and 7.4 above present AE data from pivotal study WA18221 both at the end of 12 weeks of controlled treatment in Part 1 and after 50 of all patients completed at least 1 year of treatment in Part 2 (May 10, 2010)

7.5.3 Drug-Demographic Interactions

Table 30. WA18221 AE to Wk 12 by Trial Treatment and Baseline Demographic Subgroups

WA18221 Summary of AE to Week 12 by Trial Treatment and Baseline Demographic Characteristic Subgroups (Safety Population)				
	PBO N=37	TCZ 8 mg/kg N= 37	TCZ 12 mg/kg N= 38	ALL TCZ N=75
Sex: Female, N	17	21	18	39
AEs, n	18	48	36	84
Patients with at least one AE, n (%)	10 (59)	20 (95)	16 (89)	36 (92)
Sex: Male, N	20	16	20	36
AEs, n	30	24	39	63
Patients with at least one AE, n (%)	13 (65)	13 (81)	17 (85)	30 (83)
Age: 2 – 5 years, N	11	0	16	16
AEs, n	10	0	36	36
Patients with at least one AE, n (%)	7 (64)	0	16 (100)	16 (100)
Age: 6 – 12 years, N	15	13	20	33
AEs, n	20	28	37	65
Patients with at least one AE, n (%)	10 (67)	13 (100)	15 (75)	28 (85)
Age: 13 – 18 years, N	11	24	2	26
AEs, n	18	44	2	46
Patients with at least one AE, n (%)	6 (55)	20 (83)	2 (100)	22 (85)
Ethnicity: Hispanic, N	12	7	13	20
AEs, n	10	9	25	34
Patients with at least one AE, n (%)	7 (58)	5 (71)	11 (85)	16 (80)
Ethnicity: Non-Hispanic, N	25	30	25	55
AEs, n	38	63	50	113
Patients with at least one AE, n (%)	16 (64)	28 (93)	22 (88)	50 (91)
Region: Europe, N	18	25	18	43
AEs, n	21	40	30	70
Patients with at least one AE, n (%)	10 (56)	23 (92))	14 (78)	37 (86)
Region: North America, N	8	9	7	16
AEs, n	15	24	17	41
Patients with at least one AE, n (%)	6 (75)	8 (89)	7 (100)	15 (94)
Region: South America, N	10	1	11	12
AEs, n	9	0	21	21
Patients with at least one AE, n (%)	6 (60)	0	10 (91)	10 (83)
Region: Rest of World, N	1	2	2	4
AEs, n	3	8	7	15
Patients with at least one AE, n (%)	1 (100)	2 (100)	2 (100)	4 (100)
No. of Joints: 0 to <10, N	13	8	12	20
AEs, n	19	13	23	36
Patients with at least one AE, n (%)	8 (62)	7 (88)	10 (83)	17 (85)
No. of Joints: 10 - <30, N	18	18	21	39
AEs, n	24	36	39	75
Patients with at least one AE, n (%)	12 (67)	16 (89)	18 (86)	34 (87)
No. of Joints: 30 to 71, N	6	11	5	16
AEs, n	5	23	13	36
Patients with at least one AE, n (%)	3 (50)	10 (91)	5 (100)	15 (94)
ESR: 0 to <40 mm/hr, N	14	12	9	21
AEs, n	20	24	17	41
Patients with at least one AE, n (%)	9 (64)	11 (92)	8 (89)	19 (91)
ESR: 40 to <80 mm/hr, N	15	19	17	36
AEs, n	25	36	39	75
Patients with at least one AE, n (%)	12 (80)	17 (90)	17 (100)	34 (94)
ESR: ≥ 80 mm/hr, N	8	6	12	18
AEs, n	3	12	19	31
Patients with at least one AE, n (%)	2 (25)	5 (83)	8 (67)	13 (72)
Weight: < 30 kgs, N	21	0	38	38
AEs, n	30	0	75	75
Patients with at least one AE, n (%)	16 (76)	0	33 (87)	33 (87)
Weight: ≥ 30 kgs, N	16	37	0	37
AEs, n	18	72	0	72
Patients with at least one AE, n (%)	7 (44)	33 (89)	0	33 (89)
Duration of Disease: < 4 years, N	19	16	22	38
AEs, n	22	36	41	77
Patients with at least one AE, n (%)	11 (58)	15 (94)	20 (91)	35 (92)
Duration of Disease: ≥ 4 years, N	18	21	16	37
AEs, n	26	36	34	70
Patients with at least one AE, n (%)	12 (67)	18 (86)	13 (81)	31 (84)
Oral CSs <0.3 mg/kg/day, N	19	28	10	38
AEs, n	21	55	19	74
Patients with at least one AE, n (%)	12 (63)	24 (86)	8 (80)	32 (84)
Oral CSs ≥0.3 mg/kg/day, N	18	9	28	37
AEs, n	27	17	56	73
Patients with at least one AE, n (%)	11 (61)	9 (100)	25 (89)	34 (92)
MTX Use: No, N	11	16	7	23
AEs, n	22	27	18	45
Patients with at least one AE, n (%)	8 (73)	14 (88)	6 (86)	20 (87)
MTX Use: Yes, N	26	21	31	52
AEs, n	26	45	57	102
Patients with at least one AE, n (%)	15 (58)	19 (91)	27 (87)	46 (89)

Source: WA18221 CSR, Table 50.

7.5.4 Drug-Disease Interactions

No specific drug-disease interactions have been noted in the global TCZ development program in sJIA and other indications.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies have been conducted in sJIA patients.

In adult patients, concomitant administration of a single dose of 10 mg/kg TCZ with 10 to 25 mg of MTX once weekly had no clinically significant effect on MTX exposure.

In adult patients, omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure, respectively, 1 week following a single dose of TCZ. The effect of TCZ on CYP enzymes may be clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of TCZ treatment in patients being treated with these types of medicinal products, the therapeutic monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when TCZ is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of TCZ on CYP450 enzyme activities may persist several weeks after stopping therapy.

TCZ has not been studied in combination with biological DMARDs such as TNF antagonists.

7.5.6 Safety in Escape Patients

According to protocol WA18221, during study treatment in part 1, patients were permitted to switch to open-label TCZ treatment for the specific protocol defined reasons. These patients comprise the escape population. According to the protocol, the safety data for escape patients summarized in this section includes only the data after the patients switched to escape therapy. The safety data from these patients were re-adjusted for Baseline to their first dose of TCZ and are included in the analysis for the long-term extension data cut on May 10, 2010.

The safety profile in escape patients was similar to the overall non-escape patient population in this study. The only escape patient from the blinded TCZ 8 mg/kg group to the open-label TCZ 8 mg/kg group did not report any AEs. The majority of the escape patients from placebo to TCZ treatment reported AEs: 78% in the TCZ 8 mg/kg group and 91% in the 12 mg/kg group. The reported AEs in the escape patients from placebo to TCZ were in the Musculoskeletal and Connective Tissue Disorders primarily driven by juvenile arthritis with 9 patients (45%), Infections and Infestations primarily driven by upper respiratory tract infections and various other infections with 8 patients (40%), and General Disorders and Administration Site Conditions primarily driven by pyrexia and infusion related reaction with 6 patients (30%).

Of the escape patients from placebo to TCZ treatment, 55% had AEs considered related to study treatment by the investigator. The percentage of patients escaped from placebo to either 8 or 12 mg/kg TCZ treatment who reported treatment-related AEs was similar. The majority of AEs were mild to moderate in intensity. Two patients experienced 3 severe AEs: juvenile arthritis, infusion related reaction, and MAS.

Up to 12 weeks, 50% of the escape patients from placebo to TCZ treatment had at least 1 infection AE. Of these, 1 patient escaping to TCZ 12 mg/kg treatment experienced a serious infection, pneumonia. The incidence of infection AEs was slightly higher in patients escaping from placebo to TCZ 8 mg/kg (56%) than in those escaping from placebo to TCZ 12 mg/kg (46%). However, in patients escaping to TCZ 8 mg/kg treatment, all patients reporting infection had only a single infection, while in patients escaping to TCZ 12 mg/kg treatment, 2 of the 5 patients reporting infection had 2 infection events.

Oral corticosteroids were taken ≤ 2 weeks prior to all infection AEs occurring in the escape patients. Additional analysis showed that 33% and 25% of the post-escape infection AEs resolved in ≤ 7 days and > 14 days, respectively.

Adverse events that occurred during infusions and within 24 hours after infusion AEs that occurred within 24 hours of infusions were reported in 3 escape patients, 1 patient in the placebo to TCZ 8 mg/kg escape group (AEs: oropharyngeal pain, diarrhea, and dizziness) and 2 patients in the placebo to TCZ 12 mg/kg escape group (AEs: cough and urticaria).

Two patients, both in the placebo to TCZ 12 mg/kg escape group, had AEs during infusion. One of the infusion related reactions lead to a dose interruption.

Three patients on escape treatment, all on TCZ 12 mg/kg treatment, reported 3 SAEs: pneumonia, dehydration, and MAS. These SAEs resolved following treatment. Of the 3, only MAS was considered severe and related to study treatment by the investigator.

The MAS case occurred in patient 1005, an 8-year-old female who was randomized to the placebo group and escaped at Week 2 to receive TCZ 12 mg/kg treatment. She was withdrawn from study treatment on Day 70 due to MAS. The event resolved after the Week 12 cut.

All escape patients with an infection AE had a neutrophil count ≥ LLN, and no neutropenia was reported in association with infection AEs in these patients. One escape patient experienced neutropenia but this patient did not have an infection AE. Until Week 12, none of the escape patients had a platelet count ≤ 100 × 109/L, a neutrophil count ≤ 0.5 × 109/L, or a total cholesterol value ≥ 240 mg/dL. No escape patients had an elevated bilirubin and an elevated AST or ALT during the same time window up to Week 12.

Vital signs

No pattern of clinically significant changes in vital signs or blood pressure in escape patients was observed.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

See section 7.3 for a discussion of neoplasms and malignancies in the pivotal trials.

7.6.2 Human Reproduction and Pregnancy Data

An embryo-fetal toxicity study conducted in cynomolgus monkeys showed no teratogenic potential of TCZ. A slight increase of abortion/embryo-fetal death was observed with high systemic exposure in the 50 mg/kg/day (highest dose) group (exposure > 100 times above the expected human efficacious concentration) compared with the placebo and lower dose groups. The relevance for human pregnancy is unknown.

There are no adequate data from the use of TCZ in pregnant women. No pregnancies have been reported in sJIA patients receiving TCZ in company sponsored clinical trials. There was one spontaneous (post-marketing) report of pregnancy in JIA (reported indication). The pregnancy was ongoing as of May 10th 2010 data cut. There was one report of a therapeutic abortion in a patient who became pregnant while receiving TCZ in the compassionate use program for Adult Onset Still's Disease (AOSD)/Juvenile Arthritis.

7.6.3 Pediatrics and Effect on Growth

Other than weight, growth parameters were not formally studied for the sJIA indication. As noted in Section 7.4.3, body weight analysis in study WA18221 indicated that 24% of TCZ-treated patients had a gain of body weight by more than 10% from Baseline during 12 weeks of study treatment, compared with none of the placebo-treated patients who had a gain in body weight in such a scale. No patients in any group had a loss in body weight > 10% during study treatment. The observed body weight gain in TCZ treated patients may represent a reversal of systemic complications of the disease by study treatment.

Table 31. TCZ Comparative Safety Profile: RA vs sJIA

Comparative Safety Profile: RA vs sJIA			
Characteristic	**RA**	**WA18221**	**Chugai sJIA Studies**
Total Exposure	11178 pt yrs	132 pt yrs	326 pt yrs
AE Rate	315 per 100 pt yrs	859 per 100 pt yrs	779 per 100 pt yrs
SAE Rate	15 per 100 pt yrs	25 per 100 pt yrs	32 per 100 pt yrs
Death Rate	0.5 per 100 pt yrs	0.8 per 100 pt yrs	0.6 per 100 pt yrs
Premature Withdrawal	5 per 100 pt yrs	3 per 100 pt yrs	3 per 100 pt yrs
Dose Modifications	52%	51%	data not captured
Infection AE	104 per 100 pt yrs	307 per 100 pt yrs	381 per 100 pt yrs
Infection SAE	5 per 100 pt yrs	11 per 100 pt yrs	13 per 100 pt yrs
Sampson's Criteria	<1%	<1%	data not captured
Neutropenia			
Grade 3	5%	13%	11%
Grade 4	<1%	2%	<1%
AST elevation			
Grade 3	<1%	0.90%	4%
Grade 4	<1%	0.90%	1%
ALT elevation			
Grade 3	3%	7%	7%
Grade 4	<1%	0%	2%

Source: Adapted from Summary of Clinical Safety.

Table 31 above summarizes major differences in the TCZ safety profile between sJIA and RA patients. The total exposure to TCZ in sJIA patients (132 patient-years in study WA18221 and 326 patient-years in Chugai sJIA studies) is much lower than that in RA patients (11178 patient-years). A higher overall AE rate was observed in sJIA patients (859 per 100 patient-years in study WA18221 and 779 per 100 patient-years in the Chugai sJIA studies) than in RA patients (315 per 100 patient-years). The SAE rate was also higher in sJIA patients (25 and 32 per 100 patient-years in study WA18221 and in Chugai sJIA studies, respectively) than in RA patients (15 per 100 patient-years). In both sJIA and RA patients, the death rate was < 1.0 per 100 patient-years. (0.8 per 100 patient-years in study WA18221, 0.6 per 100 patient years in the Chugai sJIA studies and 0.5 per 100 patient-years for RA patients).

The rate of premature treatment withdrawal for AE was lower in sJIA (3 per 100 patient-years in WA18221 and the Chugai studies) than in RA (5 per 100 patient-years). The incidence of study drug dose modifications was similar in the two patient populations (sJIA 51% and RA 52%).

Infection AEs were the most frequent AEs in both sJIA and RA patient populations but were higher in sJIA patients (307 per 100 patient-years in WA18221 and 381 per 100 patient years in Chugai studies) than in RA patients (104 per 100 patient-years). The infection SAE rate was also higher in sJIA (11 per 100 patient-years in study WA18221; 13 per 100 patient years) than in RA (5 per 100 patient-years).

In both pediatric patients with sJIA (based on study WA18221) and adult RA, < 1% of each patient population met the criteria of anaphylaxis according to the Sampson's analysis.

In WA18221, 13% and 2% of patients experienced CTC grade 3 and grade 4 neutropenia, respectively. 11% and <1% of patients experienced CTC grade 3 and grade 4 neutropenia, respectively, in Chugai sJIA studies. Compared with sJIA patients, CTC grade 3 (5%) and grade 4 neutropenia (< 1%) occurred less frequently in RA patients.

Grade 3 and 4 elevations in ALT/AST values were observed more often in sJIA treated with TCZ: grade 3 ALT: 7% in study WA18221 and 7% in Chugai studies; grade 3 AST: 0.9% in study WA18221 and 4% in Chugai studies; grade 4 ALT: none in study WA18221 and 2% in Chugai studies; grade 4 AST: 0.9% in study WA18221 and 1% in Chugai studies) in RA patients (grade 3 ALT: 3%, grade 3 AST: < 1%, grade 4 ALT/AST: 1%).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No TCZ overdose cases have been reported for sJIA studies. However, overdose has been reported in other studies.

Study BP19461 was a single-dose study of 2, 10, 20, 28 mg/kg TCZ in 36 male and female healthy volunteers. A total of 15 subjects were administered single doses of 20 mg/kg (10 subjects) or 28 mg/kg (5 subjects) TCZ. Three AEs were considered related to TCZ: two severe AEs of mouth ulceration and pharyngeal pain resulting from a burn on the upper palate were reported in 1 subject in the TCZ 20 mg/kg group and one mouth ulceration was reported in a subject in the TCZ 28 mg/kg group. All other AEs were mild or moderate in intensity and were considered to be not related to TCZ. There were no SAEs reported. Low neutrophil counts (< 1.5 × 109/L and a decrease of 20% below Baseline) were reported in 8 of 10 subjects dosed with TCZ 20 mg/kg and 5 of 5 subjects dosed with TCZ 28 mg/kg. In all subjects, the values recovered to within the normal range. There were no clinically relevant changes in other laboratory parameters.

In part 2 of study BP19461 (thorough QT study), single doses of TCZ (10 mg/kg and 20 mg/kg) and moxifloxacin (400 mg) were well tolerated. There were no deaths, SAEs, or AEs leading to withdrawal in this study. There was no apparent difference in the incidence of AEs between placebo and active treatment (TCZ and moxifloxacin), and the type, number, and severity of AEs reported were similar for all treatment groups.

One case of accidental overdose has been reported in which a patient with multiple myeloma was given 10 times the required dose of TCZ (40 mg/kg). This patient suffered no ill effects. No antidote to TCZ has been tested. Patients who are overdosed should be given supportive care, if necessary, and monitored closely.

Potential for abuse of TCZ is considered minimal as this is an intravenous drug administered in a monitored environment.

No specific analyses were performed for the effect of treatment withdrawal on symptom in study WA18221.

7.7 Additional Submissions

Not applicable.

8 Postmarketing Experience

8.1 Japan Post-Marketing Surveillance Program

TCZ has been approved in Japan for the treatment of sJIA and polyarticular juvenile idiopathic arthritis (pJIA) since April 16, 2008 in patients who have not responded adequately to existing therapy. TCZ was also approved in India for the treatment of sJIA and pJIA on August 28, 2008. This sBLA submission includes a summary of the serious post-marketing events reported in patients receiving TCZ for the indications of Juvenile Arthritis and AOSD.

When TCZ was approved in Japan for the treatment of sJIA and pJIA, as required by the Japanese Health Authority for all new biologics, Chugai initiated a post-marketing surveillance (JPMS) program encompassing open-label, non-comparative patient registries (sJIA: ML21940; RA and pJIA: ML21939 and its extension ML21943 and Castleman's disease: ML19367).

As of May 15, 2010, there have been 366 patients enrolled in the sJIA JPMS program (524 patient years of exposure) and 231 patients enrolled in the pJIA program (275 patient years of exposure).

In addition, there are spontaneous reports for TCZ, which originate from Japan and which derive from one of three sources:

- Reports received after the observation period of the JPMS programs (protocols ML21939, ML21940 and ML19367) and/or those events which are not followed within the long term survey (ML21943)
- RA and pJIA patients registered after 16th November 2009. Due to a notification distributed by the Japanese Health Authority, PMS programs which have already met their target number are now obligated to enroll patients on a registration only basis. Therefore, patients registered after 16th November 2009 are not observed within the protocol and are considered to be spontaneous.
- Consumer reports which originate from the drug information center (e-mail or phone) are considered to be spontaneous if the caller cannot be identified in the Chugai JPMS program as a participant.

For this sBLA submission, the Roche safety database was queried for all cases in the indications of Juvenile Arthritis and AOSD with a data cut date of May 12, 2010 (study reports including JPMS, spontaneous, and literature reports). Cases from Chugai and Roche clinical trials and compassionate use programs were then excluded for this post-marketing analysis.

There were 228 SAEs reported in 125 patients from JPMS, spontaneous and literature sources. The JPMS source includes reports for cases from the program that were reported in the literature.

There were 140 SAEs involving 72 individual patients reported from the sJIA JPMS program including 2 literature reports with 18 events (1 patient with 1 event and 1 patient with 17 events) (MCN 588086, see Section 7.3.1). There were 2 patients in this program with events with fatal outcomes (MCN 588086 and MCN 624762; see Section 7.3.1). There were 5 events in 4 patients with sJIA reported from Japanese spontaneous sources. From the rest of the world, there were 12 spontaneous events reported in 5 patients receiving TCZ for sJIA and 2 events in 2 patients reported from a drug surveillance program in the Russian Federation. There were no fatal events reported from the rest of the world for sJIA.

There were 24 events in 16 patients reported from the JPMS program for pJIA, and 4 events in 3 patients with pJIA reported from Japanese spontaneous sources. There were no fatal events in the JPMS or Japanese spontaneous pJIA population. There were no spontaneous reports outside of Japan for the indication pJIA.

There were 10 events reported in 8 patients with AOSD, including 5 spontaneous reports (5 events) and 1 literature case from Japan (3 events), one spontaneous case from India and one from Germany.

From post-marketing surveillance programs, there were 10 events reported in 4 patients. Of these 10 events, 8 were reported in 2 patients from RELACIONAR, a patient support program in Brazil; both patients (aged 14 and 45 years old) were receiving TCZ for the indication of AOSD. The 45-year-old case (MCN 678197) is further described in Section 7.3.1. The other 2 reports, as mentioned above, were for sJIA patients in the Russian Federation.

Included in the “other” category are 23 events in 13 patients reported in other juvenile arthritis indications, including: 4 events (in 4 patients) in JIA; 4 events (in 2 patients) in JRA; 9 events (in 4 patients) in AOSD; 5 events (in 2 patients) in Still-Chauffard syndrome; and 1 event in a patient receiving TCZ for the reported indication of “amyloidosis secondary to JIA”.

The MedDRA system organ classes with the largest number of reported events included Infections and Infestations (65 events), Gastrointestinal Disorders (26), Musculoskeletal and Connective Tissue Disorders (20), General Disorders and Administration Site Conditions (20), and Investigations (20). The events reported in these 5 system organ classes represent two-thirds of all the SAEs reported.

In the Infections and Infestations system organ class, there were 65 serious events reported, with the most frequently reported events being pneumonia (8), gastroenteritis (7) and bronchitis (5).

Of these events, 4 cases of pneumonia were reported in 4 patients with sJIA, 2 cases in 2 patients with pJIA and one each in AOSD and JIA. All the events of gastroenteritis occurred in individual patients with sJIA, and 3 of the 5 episodes of bronchitis occurred in 1 patient (MCN 588086).

In the Neoplasms system organ class, there were 16 reports of MAS occurring in 15 patients, 14 events in the JPMS sJIA program (1 patient had 2 episodes) and 2 events in patients with AOSD. All patients were reported as recovered or improved.

8.2 The Roche TCZ Compassionate Use Program

The Roche TCZ compassionate use program began in December 2005 as a mechanism to provide TCZ to patients with certain treatment refractory diseases that included sJIA and AOSD prior to TCZ being approved and/or marketed in a country for a specific indication. The requests for TCZ compassionate use were received from the treating physician for patients who had failed standard treatment options and demonstrated an acceptable benefit risk ratio. The TCZ treatment was provided according to local regulations.

Table 32. Demographic Data: TCZ Compassionate Use Program

	Compassionate Use Indication	
	sJIA	AOSD
Mean Age at time of first TCZ infusion, years (± S.D.)	12.6 (± 9)	36.8 (± 12)
Number of Male patients	50	8
Number of Female patients	74	19
Mean weight, kg (± S.D.)	35.8 (± 20.6)	63.5 (± 12)
Number of patients <30kg	43	0
Number of patients ≥30kg	44	12
Number of patients of unknown weight (weight not reported)	37	15

Source: Summary of Clinical Safety, Table 59.

By the clinical data entry cut-off date (May 12, 2010), 25 countries have participated in the TCZ compassionate use program in total. The relevant background demographic data for the indications of sJIA and AOSD is presented in Table 32 above. The majority of patients in the Roche TCZ compassionate use program received iv TCZ at doses of 8 or 12 mg/kg every 2 weeks.

Table 33. Line Listing of SAE in TCZ Compassionate Use Program

TCZ Compassionate Use Program: SAE Listing					
Country	Age	Sex	Event (Preferred Term)	SOC	Outcome
USA	13	M	OSTEONECROSIS	MUSC	RESOL/SEQUELAE
B	2	F	ANAPHYLACTIC REACTION	IMMUN	RESOLVED
SF	5	F	LEUKOPENIA	BLOOD	RESOLVED
GB	9	F	HYPERTENSION	VASC	RESOLVED
			RASH MACULAR	SKIN	RESOLVED
			VOMITING	GASTR	RESOLVED
I	4	M	HISTIOCYTOSIS HAEMATOPHAGIC	NEOPL	PERSISTING
			HYPOVOLAEMIC SHOCK	VASC	PERSISTING
F	27	F	ASTHENIA	GENRL	IMPROVED
			NAUSEA	GASTR	IMPROVED
			VERTIGO	EAR	IMPROVED
			HEADACHE	NERV	IMPROVED
D	9	M	WEIGHT INCREASED	INV	IMPROVED
IL	2	M	ILL-DEFINED DISORDER	GENRL	RESOLVED
N	8	F	SINUSITIS	INFEC	RESOLVED
E	19	F	HYPERSENSITIVITY	IMMUN	RESOLVED
			ARTHRITIS	MUSC	RESOLVED
IRL	22	M	INFUSION RELATED REACTION	GENRL	RESOLVED
GB	7	M	CONVULSION	NERV	RESOLVED
CH	5	M	PERICARDITIS	CARD	RESOLVED
			TOOTH ABSCESS	INFEC	RESOLVED
D	13	M	PARAESTHESIA	NERV	UNKNOWN
			DYSSTASIA	NERV	UNKNOWN
			HYPOTENSION	VASC	UNKNOWN
AUS	11	M	BLOOD CHOLESTEROL INCREASED	INV	UNKNOWN
			LOW DENSITY LIPOPROTEIN INCREASED	INV	UNKNOWN
CH	6	M	VENOUS THROMBOSIS	VASC	IMPROVED
AUS	6	M	HISTIOCYTOSIS HAEMATOPHAGIC	NEOPL	UNKNOWN
			PYREXIA	GENRL	IMPROVED
			LETHARGY	NERV	IMPROVED
			VOMITING	GASTR	IMPROVED
			COUGH	RESP	IMPROVED
			RASH	SKIN	IMPROVED
			JAUNDICE	HEPAT	IMPROVED
DK	6	F	HYPERTENSION	VASC	PERSISTING
			C-REACTIVE PROTEIN DECREASED	INV	INSUFFICIENT INFO
IL	6	M	VARICELLA	INFEC	RESOLVED
E	10	M	PETIT MAL EPILEPSY	NERV	PERSISTING
E	10	M	HISTIOCYTOSIS HAEMATOPHAGIC	NEOPL	IMPROVED
F	9	M	TENDON DISORDER	MUSC	RESOLVED
RL	18	F	HERPES ZOSTER	INFEC	RESOLVED
USA	13	M	SCAN ABNORMAL	INV	INSUFFICIENT INFO
IL	5	F	PANCREATITIS	GASTR	PERSISTING
			HYPERLIPIDAEMIA	METAB	PERSISTING
			JUVENILE ARTHRITIS	MUSC	INSUFFICIENT INFO
GB	52	M	CARDIAC FAILURE	CARD	OUTCOME DEATH
USA	13	M	HISTIOCYTOSIS HAEMATOPHAGIC	NEOPL	INSUFFICIENT INFO
D	4	F	COUGH	RESP	IMPROVED
			DYSPNOEA	RESP	IMPROVED
			ABDOMINAL DISCOMFORT	GASTR	IMPROVED
			OXYGEN SATURATION DECREASED	INV	IMPROVED
E	4.21	M	NEUTROPENIA	BLOOD	RESOLVED
			LEUKOPENIA	BLOOD	RESOLVED
E	14	M	VIRAL PERICARDITIS	INFEC	RESOLVED
I	18	F	PANNICULITIS	SKIN	INSUFFICIENT INFO

Source: Adapted from Summary Clinical Safety, page 1026.

As of May 12, 2010, 60 SAEs have been reported in 35 patients who participated in the TCZ compassionate program. Most SAEs were reported in patients with sJIA. However, 3 of the 60 SAEs (anogenital warts, MAS and osteomyelitis) were each reported in 3 patients with AOSD and 1 SAE (nephrolithiasis) was reported in 1 patient with pJIA. The majority of SAEs were resolved or improved as of May 10th 2010 data cut. There were 5 reported SAEs of MAS, 4 occurred in sJIA patients and 1 occurred in an AOSD patient. The outcomes of the MAS cases were resolved in one, improved in one, persisting in one, unknown in one, and insufficient information in one. These MAS cases were not included in the formal MAS adjudication process because of the insufficient clinical information available for evaluation at the time.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Agency review of the label submitted with sBLA 1276/22 is not complete as of the finalization of this clinical sBLA review. In brief, items identified for potential revision include the following:

(b) (4)

(b) (4)

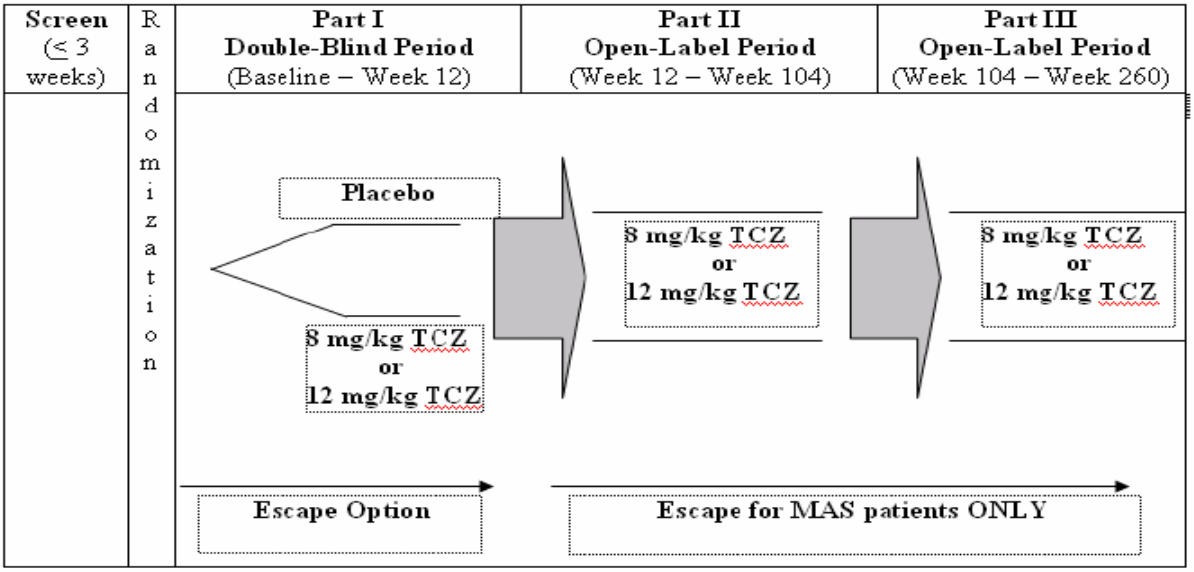
9.3 Advisory Committee Meeting

During the approval process for TCZ to treat RA, an AC meeting was held. sJIA is an unmet medical need for which the application provided substantial evidence of TCZ treatment efficacy. Potential AC members were identified in the review process. Because no new or unacceptable safety data was identified for the sJIA indication, an AC meeting was not deemed necessary. The Agency will however, hold a press briefing teleconference for the public. In addition, all previously-identified potential AC members will be notified of the details of this teleconference.

9.4 Clinical Trial Outline Study WA182218

Overall Study Design

Figure 5. WA18221 Study Schema



Source: WA18221 CSR, Figure 1, page 66.

The overall design of the study is depicted in Figure 5 above. Following screening, eligible patients were randomized into Part I of the study and received either TCZ or placebo by IV infusion in a 2:1 ratio respectively.

In the TCZ group, patients < 30 kgs received a dose of 12 mg/kg and patients ≥30 kgs received a dose of 8 mg/kg every two weeks for six doses. 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) (< 30 kgs to/from ≥30 kgs).

Patients could have their CSs tapered following the specific CS Guidelines (detailed in the clinical protocol) at Week 6 and/or Week 8 if they acquired a JIA 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 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.

Escape
The collaborative group coordinating centers; Pediatric Rheumatology Collaborative Study Group (PRCSG) and Paediatric Rheumatology International Trials Organisation (PRINTO), were used to qualify patients for escape therapy based on JIA ACR30 flare. If, in the opinion of the coordinating center a patient qualified for escape therapy:
• At a scheduled visit: treatment with open-label active study drug was administered at that visit;
• At an unscheduled visit: treatment with open-label active study drug was administered at the next scheduled visit.

Criteria for "escape" study medication were specified as the following:
1. Willingness to continue to be evaluated as per the protocol;
2. Entered escape prior to Week 12 visit for any of the following reasons:
    - Symptomatic serositis (requiring CS increase above Baseline CS dose for > 14 consecutive days or ever requiring prednisone dose > 30 mg/day or 0.5 mg/kg/day prednisone equivalent to control the serositis);
    - Persistence of fever for at least 3 consecutive days of more than 38°C, not due to infection;
    - JIA ACR30 flare compared to Baseline;
    - Any recurrence of symptomatic serositis;
    - Patients who developed MAS at or after Week 2 were considered for treatment with active TCZ in escape only after discussion between the treating physician and the Roche medical monitor.

Escape Option for Patients with High Disease Burden at Baseline

An escape option for patients with high disease burden was added as a protocol amendment and was intended to be available for study patients, but all had completed at least the Week 6 assessment before Protocol Version B was implemented and approved. If a patient could not meet the above JIA ACR30 flare criteria due to a high disease burden at study entry, they were permitted to enter escape at the Week 6 visit only if all of the following conditions were met:

- If at Baseline the patient entered the study with polyarticular disease (≥ 5 active joints) and no fever (defined as a temperature > 38°C);
- If any two of the five Baseline non-laboratory JIA ACR core set components were so severe they could not worsen by 30%:
- Physician global assessment of disease activity visual analogue scale (VAS): ≥ 77 / 100 mm;
- Parent global assessment of well-being VAS: ≥ 77 / 100 mm;
- Number of joints with active arthritis: ≥ 55 / 71;
- Number of joints with limited range of motion: ≥ 52 / 67;
- CHAQ-DI score: ≥ 2.31 / 3;
- At Week 6, there had not been a JIA ACR30 improvement

Patients who entered escape and did not achieve significant clinical improvement after three doses of TCZ were considered for discontinuation of TCZ. The reason for escape therapy had to be recorded as an AE in the electronic case report form (eCRF) with the start date being the first date escape therapy was given, whether it was with steroids, other permitted escape concomitant treatments, or open-label active study drug. Not all of the escape options allowed by the protocol were utilized, and other reasons for escape therapy, not defined in the protocol are discussed in the results.

Patients who continued in the study but qualified for escape and received escape treatment were offered the option to be treated with open-label TCZ in addition to standard of care (may include IV CSs or increased oral doses of prednisone above Baseline). No additional DMARDs or biologics were permitted for patients (without MAS) in the escape group. Patients < 30 kgs received 12 mg/kg and those ≥ 30 kgs received 8 mg/kg TCZ respectively, every two weeks for a minimum of three doses. The collection of clinical, laboratory, and safety data continued every two weeks for these patients on these dose-regimens in the escape group.

Inclusion Criteria

1. Age 2 up to and including 17 years at screening into trial;
2. Systemic Juvenile Idiopathic Arthritis according to ILAR classification (2001);
3. More than 6 months of documented persistent sJIA activity prior to screening (not requiring 6 months from formal diagnosis) including an inadequate response to NSAIDs and corticosteroids due to toxicity or lack of efficacy.
4. Presence of active disease as determined by the presence of :
    - ≥5 active joints at screening and baseline, (with sufficient diary temperature entries to appropriately identify the presence or absence of fever, 14 days of temperature recordings required) or

- ≥2 active joints at screening and baseline and fever >38°C for at least 5 out of any 14 consecutive days during screening and receiving prednisone or equivalent at a stable dose at no more than 0.5 mg/kg/day or 30 mg/day, whichever is less.

During this same time period the corticosteroid dose continues unchanged. Under these circumstances a patient does not need to complete a full 14 days of temperature diary entries to meet this inclusion criteria.

5. hsCRP > 4.3 mg/L or 0.43 mg/dl (1.5 x ULN (ULN= 0.28 mg/dl));
6. Recovered from any symptomatic serositis for at least one month prior to the screening visit, and requiring dose of corticosteroids ≤ than 30 mg/day or 0.5 mg/kg/day, whichever is less, at baseline
7. Fertility:
   - Female not of child-bearing potential, or Female of child-bearing potential practicing effective contraceptive measures, having a negative urine pregnancy test within three weeks prior to randomization; OR
   - Sterile male, OR
   - Non sterile male practicing effective contraceptive measures with female partner of child-bearing potential.

   [Females of childbearing potential must be using a reliable means of contraception (abstinence being a possible option) throughout the study and up to 12 weeks after the last infusion of study drug].
8. Must meet one of the following:
   - not receiving MTX, or discontinued MTX at least 4 weeks prior to baseline visit, OR
   - taking MTX for at least 12 weeks immediately prior to the baseline visit and on a stable dose of ≤20 mg/m^2 for at least 8 weeks prior to the baseline visit, together with either folic acid or folinic acid according to local standard of care.

   9. Never treated with biologics or, if previously treated with biologics, discontinued etanercept ≥ 2 weeks, infliximab or adalimumab ≥ 8 weeks, anakinra ≥1 week, or abatacept ≥ 12 weeks prior to the baseline visit;
10. Not currently receiving oral CS, or taking oral CS at a stable dose for a minimum of 2 weeks prior to the baseline visit at no more than 30 mg/day or 0.5 mg/kg/day whichever is less;
11. Not taking NSAIDs, or taking no more than 1 type of NSAID at a stable dose for a minimum of 2 weeks prior to the baseline visit and is less than or equal to the maximum recommended daily dose;
12. Written informed consent for study participation obtained from parents or legal guardian, with assent as appropriate by the patient, depending on the level of the patient's understanding;
13. Parental or guardian written agreement to comply with the requirements of the study protocol.

Exclusion Criteria

Presence of any of the following will exclude the patient:

<u>General</u>

1. Wheelchair bound or bedridden;
2. Any other auto-immune, rheumatic disease or overlap syndrome other than sJIA;
3. Not fully recovered from recent surgery or less than six weeks since surgery, at the time of screening visit; or planned surgery during the initial 12 weeks of the study;

4. Lack of peripheral venous access;

General Safety

1. Pregnant, lactating, or intending to become pregnant during study conduct and up to 12 weeks after the last administration of study drug;
2. Any significant concurrent medical or surgical condition which would jeopardize the patient's safety or ability to complete the trial;
3. History of significant allergic or infusion reactions to prior biologic therapy;
4. Inborn conditions characterized by a compromised immune system;
5. Known HIV infection or other acquired forms of immune compromise;
6. History of alcohol, drug or chemical abuse within 6 months of screening;
7. Evidence of serious uncontrolled concomitant diseases including but not limited to the nervous system, renal, hepatic or endocrine;
8. Asthma for which the patient has required the use of oral or parenteral corticosteroids for ≥ 2 weeks within 6 months prior to the baseline visit;
9. Any active acute, subacute, chronic or recurrent bacterial, viral or systemic fungal infection including but not limited to:
    a) acute or chronic renal / bladder infections,
    b) acute or chronic pulmonary infections;
10. History of atypical tuberculosis;
11. Active TB requiring treatment within 2 years prior to screening visit;
12. Positive PPD at screen, unless treated with anti-tuberculosis therapy for at least 4 weeks prior to receiving study medication and chest radiograph is negative for active tuberculosis;
13. Any major episode of infection requiring hospitalization or treatment during screening or treatment with IV antibiotics completing within 4 weeks of the screening visit or oral antibiotics completing within 2 weeks of the screening visit;
14. History of reactivation or new onset of a systemic infection such as herpes zoster or Epstein Barr virus within 2 months of the screening visit;
15. Hepatitis B surface Ag or hepatitis C Ab positive;
16. Chronic hepatitis – viral or autoimmune;
17. Significant cardiac [e.g. congenital heart disease, valvular heart disease, constrictive pericarditis (unrelated to systemic JIA), myocarditis] or pulmonary disease, (e.g. asthma, cystic fibrosis);
18. History or concurrent serious gastrointestinal disorders such as ulcer or inflammatory bowel disease, Crohn's disease, ulcerative colitis or other symptomatic lower gastrointestinal conditions, including ulcer and perforation;
19. History of or current cancer or lymphoma;
20. Uncontrolled diabetes mellitus defined as Hgb A1c > 8.8 mg/dL;
21. History of macrophage activation syndrome within 3 months prior to the screening visit;

Excluded Previous or Concomitant Therapy

1. Participation in another interventional clinical trial within the past thirty days or five serum half-lives or the pharmacodynamic effect of the investigative medication, whichever is longer;
2. Previous treatment with tocilizumab;
3. Intra-articular, intramuscular, intravenous or long-acting (such as dexamethasone) corticosteroids within 4 weeks prior to the baseline visit;

4. Treatment with DMARDs (other than MTX) or immunosuppressants, including but not limited to: hydroxychloroquine, chloroquine, gold, azathioprine, D-penicillamine, sulfasalazine, cyclosporine or thalidomide within 6 weeks prior to the baseline visit;
5. Treatment with leflunomide which was not followed by standardized cholestyramine washout and documented to be below the limit of detection prior to the baseline visit;
6. Treatment with cyclophosphamide within 3 months prior to the baseline visit;
7. Treatment with etoposide (VP16) within 3 months prior to the baseline visit;
8. Treatment with growth hormone within 4 weeks prior to the baseline visit;
9. Treatment with androgens (e.g. testosterone) within 4 weeks prior to the baseline visit;
10. Treatment with a statin within 3 months prior to the baseline visit;
11. Administration of intravenous immunoglobulin within 4 weeks prior to the baseline visit;
12. Previous treatment with any cell depleting therapies, including investigational agents (e.g. anti-CD19 and anti-CD20);
13. Prior stem cell transplant at any time;
14. Live or attenuated vaccines within 4 weeks prior to the baseline visit, or intending to receive while on study medication or 12 weeks following the last dose of study medication;

Laboratory Exclusions at Screening
1. Serum creatinine >1.5 ULN (upper limit of normal for age and sex);
2. AST or ALT > 1.5 ULN (upper limit of normal for age and sex);
3. Total bilirubin > 1.3 mg/dL (> 23 umol/L);
4. Platelet count < $150x10^3/\mu L$ (< $150,000/mm^3$);
5. Hemoglobin < 7.0 g/dL (< 4.3 mmol/L);
6. WBC count < $5,000/mm^3$ (< $5.0x\ 10^9/L$);
7. Neutrophil count < $2,500/\ mm^3$ (< $2.5x\ 10^9/L$);
8. Fibrinogen < 200 mg/dL (normal range 200-400 mg/dL)

Concomitant Medications

A concomitant medication was defined as any drug or substance taken during the study period regardless of route of administration. This included any preventative vaccines (eg, tetanus or flu vaccines) that the patient received during the course of this study. All concomitant medications (including over-the-counter medications, herbals, vitamins, and food supplements) and procedures were recorded in the eCRF.

Concomitant Medications and Treatments for sJIA

DMARDs
• MTX was permitted but not required during this study. If a patient had been on MTX in the past, they must have discontinued MTX at least 4 weeks prior to the Baseline visit. Those patients receiving MTX had to have been taking MTX for at least 12 weeks immediately prior to the Baseline visit and received a stable dose of ≤ 20 mg/m^2 for at least 8 weeks prior to the Baseline visit, together with at least the minimum recommended dose of either folic acid or folinic acid according to the local standard of care. During the study, the MTX dose could be decreased, if applicable, at any time in Part I for documented reasons of safety but not for efficacy (i.e., following improvement in symptoms).

• Leflunomide was not allowed during the study.
• Cyclophosphamide was not permitted during study or within 3 months prior to Baseline visit.
• Etoposide (VP16) was not permitted during the study or within 3 months prior to Baseline visit.
• Treatment with DMARDs other than MTX and immunosuppressants had to have been discontinued 6 weeks prior to Baseline visit and were not permitted during study conduct. These included, but were not limited to the following:

- Hydroxychloroquine;
- Chloroquine;
- Gold;
- Azathioprine;
- D-penicillamine;
- Sulfasalazine;
- Cyclosporine;
- Thalidomide.

Biologics
For patients who previously received biologics as follows:

• Etanercept had to be discontinued ≥ 2 weeks prior to Baseline and was not permitted during study conduct;
• Anakinra had to be discontinued ≥ 1 week prior to Baseline and was not permitted during study conduct;
• Abatacept had to be discontinued ≥ 12 weeks prior to Baseline and was not permitted during study conduct;
• Infliximab or Adalimumab had to be discontinued ≥ 8 weeks prior to Baseline and was not permitted during study conduct.
• Patients previously treated with TCZ were not permitted in the study.

Steroids
Patients who were not currently receiving CSs or were taking oral CSs at a stable dose for a minimum of 2 weeks prior to the Baseline visit at no more than 30 mg/day or 0.5 mg/kg/day, whichever was less were allowed in the study.

Intra-articular, intramuscular, IV, or long-acting (such as dexamethasone) CSs within 4 weeks prior to the Baseline visit were not allowed in the study. Injection of intra-articular CSs while on blinded study medication (Part I) was strongly discouraged as it could adversely effect escape or CS reduction criteria or study endpoints.

During the first 12 weeks of the study (Part I), reductions in CS were allowed only if the specific criteria were met to be eligible for these CS reductions. CSs could be increased for reasons of safety (e.g., asthma attack, serositis) to a maximum of 30 mg/day or 0.5 mg/kg/day prednisone or equivalent, whichever was less, for a maximum dosing period of < 14 days after which the CS dosage had to be returned to Baseline according to the Appendix 8 in the Protocol.

NSAIDs

Patients who were not taking NSAIDs, or taking no more than one type of NSAID at a dose that had remained stable for ≥ 2 weeks prior to the Baseline visit and was less than or equal to the maximum recommended daily dose, were included in the study. The dose of NSAID had to remain stable throughout the double-blind period of the study (Part I). The dose could be lowered for documented reasons of safety and only tapered for efficacy after any CSs and MTX had been discontinued and the patient had been in clinical remission for at least six months.

Immunoglobulin
Administration of IV immunoglobulin was not permitted during the study or within 4 weeks prior to the Baseline visit.

For active varicella infection (chickenpox) or significant exposure to varicella zoster infection in a patient without history of chickenpox (varicella IgG titer available from screening), varicella zoster immunoglobulins could be given at the discretion of the investigator.

Acetaminophen (paracetamol) and other analgesics
Normal release acetaminophen (not extended release) was used for pain as required. Analgesics could not be taken within 6 hours prior to a visit where clinical efficacy assessments were performed. The administration of analgesics had to be recorded in the eCRF.

Iron
Iron could be administered to patients determined to be anemic at screening based on the opinion of the investigator that the anemia was likely due to anemia of chronic inflammation (disease) or iron deficiency and iron was likely to be beneficial without contraindication for its use.

Folic Acid
Patients who received MTX as part of background treatment during the study had to receive at least the minimum recommended dose of folic acid or folinic acid weekly as per local standard of care.

Topical Anesthesia
Topically applied anesthetic creams such as Eutectic Mixture of Lidocaine and Prilocaine (EMLA) were permitted at sites of potential IV sites and venipunctures based on local guidelines.

Other Medications and Treatments

Vaccines: Live or attenuated vaccines were not permitted within 4 weeks of the Baseline visit, during study conduct, or within 12 weeks following the last administration of study medication.
Statins: Statins were not permitted within 3 months prior to the Baseline visit or during the first 26 weeks of the study.
Growth hormone: Growth hormone was not permitted within 4 weeks prior to the Baseline visit or during the entire study.
Androgens: Androgens (e.g., testosterone) were not permitted within 4 weeks prior to the Baseline visitor during the entire study.

Cell depleting therapies: Previous treatment with any cell depleting therapy, including any investigational agents (e.g., anti-CD19 and anti-CD20) was not permitted in the study.
Stem cell transplant: Patients with a history of prior stem cell transplant at any time were not permitted in the study.

Assignment to Treatment Group

It was planned that 108 patients would be unequally randomized (TCZ: placebo = 2:1), providing approximately 72 TCZ-treated patients and 36 placebo-treated patients. A total of 112 patients were ultimately randomized. Randomization was performed by a central randomization service IVRS and was stratified by BW, disease duration, background CS dose, and background MTX use in order to achieve a reasonable balance for prognostic features that affect efficacy and/or safety in the two treatment groups.
Each factor had two levels as follows:
• BW: < 30 kgs or ≥ 30 kgs;
• Disease duration: < 4 years or ≥ 4 years;
• Background CS dose: < 0.3 mg/kg or ≥ 0.3 mg/kg;
• Background MTX use: Yes or No.
The patient randomization numbers generated by Roche or its designee were given to the investigator over the telephone at the time of individual patient enrollment. The investigator or designee entered a pre-defined patient number in the eCRF and entered the corresponding patient randomization number for allocation to the treatment groups in the appropriate place on each patient's eCRF. The patient randomization numbers were allocated sequentially in the order in which the patients were enrolled according to the specification document agreed with the external randomization company for allocation to the treatment groups.

Blinding

This was a blinded study, with the sponsor, investigators, and patients unaware of the treatment assignment of each patient at randomization into Part I. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication or independent pharmacological analysis of biological samples was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment. Unblinding was performed by means of the IVRS. Written documentation followed any verbal request to unblind a patient's treatment.

Roche unblinded the identity of the study medication for all suspected unexpected SAEs that were considered by the investigator to be related to study drug as per safety reference documents; Investigators Brochure, Core Data Sheet, and Summary of Product Characteristics (SmPC). Any unblinding for independent pharmacological analysis of biological samples including any PK, PD data, or ongoing safety monitoring by a DSMB were performed according to procedures in place to ensure integrity of the data. All other individuals directly involved in this study at Roche remained blinded until after the database lock of study Part I.

Drug Administration

The TCZ and placebo vials were stored at a temperature of 2-8ºC. The infusion bag of study medication (after it had been prepared) could have been stored at 2-8ºC for 24 hours providing that the infusion was prepared aseptically and allowed to return to room temperature before administration (one to two hours depending on ambient room temperatures). In study Part I, patients could have their study medication prepared in advance, but had to have assessments completed and coordinating center feedback prior to the administration of study medication due to possible changes in study medication required for escape.

The TCZ or placebo was administered at room temperature by controlled infusion into a vein over a one hour period. For a 100 mL infusion bag, the initial infusion speed was 10 mL/hr for 15 minutes and then increased to 130 mL/hr to complete the dosing over approximately one hour. For a 50 mL infusion bag, the initial infusion speed was also 10 mL/hr for 15 minutes and then increased to 65 mL/hr. In order to flush the remaining study medication through the IV set, 20 mL of normal saline for patients ≥ 30 kgs and 10 mL for patients < 30 kgs was administered following the infusion of study medication.

In the event that a patient randomized into Part I of the study with adequate peripheral venous access as required unexpectedly lost this access, and was unable to continue participation without intervention, central venous access was considered and discussed with the medical monitor prior to implementation.

Criteria for Withdrawal from Treatment or Study and Replacement Policy

Parents/legal guardians had the right to withdraw their child from the study at any time for any reason including the criteria of withdrawing the informed consent or lost to follow-up. The parents/legal guardians were asked if they could be contacted for further information. Patients who discontinued study participation and withdrew consent were not required to return for any follow-up assessments. However, if the patient decided to withdraw from the study, all efforts were made to complete and report the observations prior to withdrawal as thoroughly as possible. The outcome of the premature withdrawal discussion was documented in both the medical records and in the eCRF. If lost to follow-up, the investigator should contact the patient's parents/legal guardians or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal was made with an explanation of why the patient withdrew from the study.

Patients prematurely discontinued from the study for any reason were not replaced.

TCZ was to be permanently discontinued if any of the following occurred:

- A reaction that resulted in bronchospasm with wheezing and/or dsypnea requiring ventilatory support, or symptomatic hypotension with a significant decrease in blood pressure during or following study agent infusion;
- Opportunistic infection;
- Malignancy;

• Pregnancy, positive pregnancy test or pregnancy planned within the study period or within 6 months after last TCZ infusion;
• The initiation of Protocol prohibited medications as described above
• Congestive heart failure;
• Patient was deemed ineligible for the following tuberculosis (TB) criteria:
  - A diagnosis of active TB was made;
  - A patient who was receiving treatment for latent TB discontinued this treatment prematurely or was noncompliant with this therapy;
  - A patient had symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or had recent close contact with a person with active TB and could or would not continue additional evaluation;
• A reaction suggestive of serum sickness and not representative of signs and symptoms of any other recognized clinical syndromes that occurred up to 14 days following TCZ administration. This reaction could result in myalgia and/or arthralgia with fever and/or rash that could be accompanied by other events including pruritis, facial, hand or lip edema, dysphagia, urticaria, sore-throat, and headache;
• The investigator or Roche's medical monitor deemed that it was in the patient's best interest;
• Any AE that in the opinion of the investigator or the sponsor precluded further study medication administration;
• If three consecutive doses of study medication were missed due to abnormal LFTs (ALT and AST);
• Two consecutive total bilirubin values taken at least one week apart > 3 mg/dL;
• Permanent discontinuation of study agent infusions was considered for patients who developed a severe infusion reaction or serious infection.

All patients who permanently discontinued study medication infusions but had not terminated study participation had to have evaluations, including all withdrawal visits, as shown in the schedule of assessments (Table 34 below). If the reason for removal of a patient from the study was an AE, the principal specific event was recorded on the eCRF. The patient was not, if possible, withdrawn from the study but only from the study medication and was to be followed until the AE had resolved, if possible.

Dose Modification/Interruptions

Dose interruptions/modification rules for patients receiving double-blind study treatment or escape therapy were as follows:

Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) Elevations:
If a patient had a post-Baseline ALT or AST elevation > 3 and < 5 x Upper limit of Normal (ULN), dosing with TCZ was continued based on clinical judgment and if the ALT or AST elevation was thought to be an isolated event. NSAIDs or MTX could be temporarily withheld or reduced and weekly LFTs continued.

If a patient had a post-Baseline ALT or AST elevation > 5 x ULN, dosing with TCZ,

MTX, or other hepatotoxic medications (e.g., INH) could be withheld, NSAIDs reduced, and LFTs repeated weekly:
• If repeat ALT and/or AST < 3 x ULN, TCZ dosing resumed with weekly LFTs continued until < 1.5 X ULN and then MTX and other hepatotoxic medications resumed until ALT or AST < 1.5 X ULN;
• If repeat ALT or AST elevation > 3 and/or < 5 x ULN, TCZ dosing resumed based on clinical judgment and if the ALT or AST elevation was considered to be an isolated event. Weekly LFTs continued until ALT or AST < 1.5 X ULN;
• If repeat ALT and/or AST elevation > 5 x ULN, TCZ was not given and NSAIDs were reduced or held and weekly LFTs continued until ALT or AST < 1.5 X ULN.
If three consecutive scheduled doses of study medication were missed because of an elevated ALT or AST, then the patient was discontinued from the study medication.

Bilirubin Elevation
If total bilirubin > 3 mg/dl:
• Study medication was stopped;
• One week later bilirubin and LFTs (including AST, ALT) were repeated;
• If bilirubin persisted > 3 mg/dl study medication was permanently stopped;
• If bilirubin returned to < ULN then TCZ infusions continued.

Hematology Abnormalities
Study medication dosing was delayed if the:
• Absolute White Blood Cell (WBC) count was < 3,500/mm3;
• Absolute neutrophil count was < 1,500/mm3;
• Platelet count was < 150,000/mm3.
A repeat blood sample was taken just prior to the next dose of study medication to verify that hematology values were above the minimum values required for dosing.

Infections
If a patient developed a new infection while undergoing treatment with study medication the infusions were monitored closely. Study medication infusions were not given to a patient with a clinically important active infection but, if possible, the patient could still come in for all visit assessments. If a patient developed a serious infection then discontinuation (temporary or permanent) was considered. For active varicella infection (chickenpox) or significant exposure to varicella zoster infection in a patient without history of chickenpox (varicella IgG titer available from screening), study treatment was interrupted until the investigator was sure that the symptoms had resolved or that no active infection was present. Treatment with varicella zoster immunoglobulins was given at the discretion of the investigator.

Infusion Reactions

Any AEs that occurred during infusion or within 24 hours after infusion were recorded as AEs in the eCRF.

Medications for the treatment of hypersensitivity reactions were available for immediate use in case of a severe hypersensitivity reaction. These included acetaminophen, antihistamines, CSs, and adrenaline.

Signs of a possible infusion reaction included fever, chills, pruritis, urticaria, or cardiopulmonary reactions including but not limited to chest pain, dyspnea, hypotension, or hypertension. If any of the above signs and symptoms were observed during the infusion and the patient remained with stable cardiovascular status:

- The infusion rate was slowed down (at least halved) and the infusion time extended;
- If the patient continued to display signs and symptoms of hypersensitivity, an intramuscular or slow IV dose of an antihistamine was administered;
- After an infusion reaction had been documented antihistamines and or acetaminophen could be administered prophylactically prior to subsequent infusions if desired by the investigator to try to prevent reoccurrence of mild to moderate infusion reactions.

In patients who experienced severe infusion reactions with cardiovascular collapse:

- The study medication was permanently discontinued;
- The patient was treated as for an anaphylactic reaction with IV antihistamines, CSs and adrenaline if necessary;
- A sample for the presence of anti-TCZ antibodies was obtained;
- No further study medication would be given but the patient could remain in the study and followed the procedures outlined in the protocol (i.e. Patients and/or parents/legal guardians who discontinue study medication infusions and are not terminating study participation should return for all withdrawal visits)

Schedule of Assessments

Table 34. Study WA18221 Schedule of Assessments (Part I)

VISIT	Screen - 3 weeks	Baseline Visit 1	Lab[24]	Lab[24]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Lab[24]	Visit 7/ **WD1**[21]
Study Day	-21	1	3	8	15	29	43	57	71	78	85
Weeks from Baseline ± 3 days	- 3 weeks	0	0-1	1	2	4	6	8	10	11	12
Informed Consent[1]	X										
Assessments											
Inclusion/Exclusion	X	X									
Medical History[2]	X	X									
Demographics	X										
Concomitant Meds	X	X			X	X	X	X	X		X
Safety Assessments											
ECG[3]	X										
PPD[4]	X										
CXR[5]	X										
Infusions[6]		X			X	X	X	X	X		X
Clinical Assessments											
Height(Stadiometer)/ Weight	X	X			X	X	X	X	X		X
Vital Signs[25]	X	X			X	X	X	X	X		X
Physical Exam	X	X									X
Joint Count	X	X			X	X	X	X	X		X
Pt/Parent Global	X	X			X	X	X	X	X		X
Physician Global	X	X			X	X	X	X	X		X
CHAQ	X	X			X	X	X	X	X		X
Tanner Score	X										
CHQ		X									X
JADI[7]		X									
Inactive Disease[19]											X
PA Wrist Hand Xrays[8]		X									

VISIT	Screen - 3 weeks	Baseline Visit 1	Lab[24]	Lab[24]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Lab[24]	Visit 7/**WD1**[21]
Study Day	-21	1	3	8	15	29	43	57	71	78	85
Weeks from Baseline ± 3 days	- 3 weeks	0	0-1	1	2	4	6	8	10	11	12
Safety											
Adverse Events		X	X	X	X	X	X	X	X	X	X
Safety Labs											
Fasting Labs[9]		X	X	X	X		X				X
Screening Labs	X										
Hematology	X	X		X	X	X	X	X	X		X
Reticulocytes		X		X	X	X	X				
Pregnancy(urine)[11,13]	X	X			X	X	X	X	X		X
Blood Chemistry	X	X			X	X	X	X	X		X
Immunology Profile		X									X
Urinalysis dipstick[13]		X			X	X	X	X	X		X
Fibrinogen/D-Dimer		X			X	X	X	X	X		X
Lipid Profile[23]		X			X						X
Lab Assessments											
ESR[12]		X			X	X	X	X	X		X
Acute Phase Reactants		X	X	X	X	X	X	X	X		X
Iron		X[22]									

VISIT	Screen - 3 weeks	Baseline Visit 1	Lab[24]	Lab[24]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Lab[24]	Visit 7/ WD1[21]
Study Day	-21	1	3	8	15	29	43	57	71	78	85
Weeks from Baseline + 3 days	- 3 weeks	0	0-1	1	2	4	6	8	10	11	12
Lab Assessments (Continued)											
IGF-1 system		X	X	X	X						X
Bone markers		X	X	X	X						X
Serum hepcidin/urineβ-2 microglobulin[13]		X	X	X	X		X				X
Fasting insulin, glucose, C peptide[17]		X					X				
Sex hormones (children ≥ 30kg)		X									X
PK/PD:TCZ, IL-6, sIL-6R[14,15]		X[14,15]		X[16]	X[14,15]	X[14,15]	X[14]	X[14]	X[14,15]	X[16]	X[14]
Anti-TCZ antibodies(HAHA)		X[15]									X[14]
Inflammation/ Cytokine Profile[23]		X					X				
BSR protein[18]		X					X				

[1] The parent (or patient if they had reached the legal age of consent, and if applicable at the site) must sign and date an informed consent form before any study related activities can occur
[2] Medical History to include information on prior immunization/vaccines and growth velocity
[3] At screening 2 ECG's were obtained 2-5 minutes apart. At least 2 minutes must separate the recording of the two
[4] Purified Protein Derivative (PPD) was interpreted based on local guidelines for immunosuppressed patients.
[5] Chest radiograph were utilized for screening purposes if obtained within 90 days prior to Baseline.
[6] All assessments (safety, clinical, laboratory) except as noted were completed prior to start of infusion. If a severe infusion reaction felt to be anaphylactic or anaphylactoid in nature was suspected a blood sample for anti-TCZ antibodies was obtained.
[7] JADI score consisted of two parts-part A-articular and part E extraarticular-each with separate score
[8] PA Standard Both Wrists and Hands (total two radiographs-one radiograph for combined L wrist and hand and one radiograph for R wrist and hand). Radiograph was optional (based on site decision) and was only to be obtained if site had requested and received IRB/EC approval and written informed consent obtained from parent/legal guardian. It was to be obtained within 4 weeks following Baseline and within ± 4 weeks other time points in Schedule of Assessments
[9] Fasting Labs after minimum 8 hour fast

Source: WA18221 CSR, Table 3, pages 86-89.

Efficacy Parameters

Primary efficacy parameter:

The primary endpoint of Part I was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR30 response) at Week 12 and absence of fever*
**Absence of fever was defined as no diary temperature recording ≥37.5° C in the preceding seven days*

Secondary efficacy parameter:

Part I - Secondary Endpoints:

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 with normal CRP at Week 12;
5. The percentage change from Baseline (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 VAS at Week 12;
10. The proportion of patients with anemia at Baseline who increase Hgb ≥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 of JIA at Baseline 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 leukocytosis 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.

Major Amendments

The Protocol was amended once and the amendment was implemented during the conduct of the study. A list of the main Protocol changes is as follows:

First Amendment – Protocol Version B June 2009. 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. Many of the changes were to correct ambiguous or incorrect wording and to improve clarity and included the following:

- Updated disease definitions including sJIA disease and MAS;
- Changed the study weeks on active treatment (open-label) with unblinded independent joint assessor (Week 12 to and including Week 104) for Part II;
- Clarified the inclusion and exclusion criteria;
- Updated treatments allowed and prohibited for sJIA;
- Updated the withdrawal requirements for patients and discontinuation criteria if patients did not achieve a JIA ACR 30 response;
- Extended the length of the study design from a two-part, 3 year study to a three-part, 5 year study;
- Clarified the visits and weeks of Part I – the double-blind portion of the study to evaluate efficacy and safety;
- Changed the day of the Baseline score taken as the pre-dose assessment at Visit 1 (the day of the first infusion of study drug) to Day 1 from Day 0;
- Updated the timing of reporting to Roche with local serum ferritin results ≥ 3,000 nanograms/milliliter (ng/mL);
- Clarified the definition of improvement in JIA and Tanner Stage;
- If at least two consecutive TCZ infusions were missed for safety reasons, quantitative

Ig and PK/PD assessments (IL-6, TCZ, sIL-6R and anti-TCZ antibodies) were performed pre-dose at the next scheduled visit and pre-dose 2 weeks later;
• Included responsibility and specific guidance for steroid tapering during and after escape therapy;
• Added the escape option to allow children with more severe disease at Baseline an opportunity to escape and receive active open-label study drug;
• To allow varicella zoster immunoglobulin upon exposure to chicken pox in children who had not had chicken pox;
• Clarified safety parameters and thus improved safety monitoring and reporting.

Protocol Violations

Table 35. WA18221 Protocol Violations to Week 12

Study WA18221 Protocol Violations up to Week 12				
	PBO	TCZ 8 mg/kg	TCZ 12 mg/kg	ALL TCZ
Number of Patients Randomized	37	37	38	75
Number of Patients Included in PER PROTOCOL	31	32	32	64
Number of Patients Excluded in PER PROTOCOL	6	5	6	11
RECEIVED ORAL CS > 30 OR > 0.5 MG/KG/DAY AT ANY TIME DURING THE STUDY	2	1	3	4
MISSED THE I.V. INFUSION OF STUDY MEDICATION AT WEEK 10	2	1	2	3
NOT CURRENTLY RECEIVING ORAL CSS, OR TAKING ORAL CSS AT A STABLE DOSE FOR >= 14 DAYS PRIOR TO BASELINE <= 30 <= 0.5 MG/KG/DAY	0	1	2	3
PATIENTS JOINT ASSESSOR NO LONGER BLINDED TO CLINICAL STATUS AT WK 12	1	1	1	2
EDIARY TEMPERATURE NOT RECORDED >/=4 OF 7 DAYS BEFORE WK 12 ASSESSMENT	1	1	0	1
ESCAPED WITHOUT A VALID REASON	1	1	0	1
DMARDS AT ANY TIME DURING THE STUDY	1	1	0	1
IA, IM OR IV CSS WITHIN 28 DAYS BASELINE VISIT	0	1	0	1
JIA ACR CORE SET COMPONENTS ASSESSED OUTSIDE OF THE DRAM SPECIFIED VISIT WINDOW OF THE SCHEDULED WEEK 12 VISIT I.E. +/- 6 DAYS AROUND NOMINAL STUDY DAY	0	1	0	1
PATIENTS WHO RECEIVED IM OR IVCSS AT ANY TIME DURING THE STUDY	0	0	1	1
PRESENCE OF ACTIVE DISEASE	0	0	1	1
TREATMENT WITH ANTI-TNF THERAPIES OR OTHERBIOLOGIC AT ANY TIME DURING THE STUDY	0	0	1	1
ADMINISTRATION OF INTRAVENOUS IMMUNOGLOBULIN DURING STUDY	1	0	0	0
ANY OTHER AUTO-IMMUNE, RHEUMATIC DISEASE OR OVERLAP SYNDROME OTHER THAN SJIA	1	0	0	0
CRP <= 4.3 MG/L	1	0	0	0
PATIENTS WHO HAD A QUALIFYING REASON FOR ESCAPE BUT DIDN'T ESCAPE	1	0	0	0

Source: WA18221 CSR, Table 6.

Table 36. Line Listing of Patients Excluded from WA18221 Analysis

Listing of Patients Excluded from Analysis Populations at Week 12				
Patient No.	**Age (yr)**	**Sex**	**Excluded From**	**Reason for Exclusion**
1052	3	F	PER PROTOCOL	Joint Assessor no longer blinded to clinical status at Wk 12
			PER PROTOCOL	Received oral CS > 30 mg/d or >0.5 mg/kg/d at any time during study
1662	15	F	PER PROTOCOL	CRP </=4.3 mg/L
1685	11	M	PER PROTOCOL	Qualifying reason for escape byt not escaped
1702	14	F	PER PROTOCOL	Any other auto-immune, rheumatic dz or overlap syndrome other than sJIA
			PER PROTOCOL	Patients who escaped without a valid reason
			PER PROTOCOL	Received oral CS > 30 mg/d or >0.5 mg/kg/d at any time during study
1005	8	F	PER PROTOCOL	IV Immunoglobulin not permitted during study
			PER PROTOCOL	Ediary temperature not recorded on 4 or> of 7 days preceding Wk 12
			PER PROTOCOL	Missed IV infusion of study medication at Wk 10
			PER PROTOCOL	Treatment with DMARDS at any time during the study
1342	13	M	PER PROTOCOL	Missed IV infusion of study medication at Wk 10
1094	11	M	PER PROTOCOL	JIA core set assessed outside dram specified visit window
			PER PROTOCOL	Not currently on oral CSS or taking at stable dose >/=14 days
			PER PROTOCOL	Missed IV infusion of study medication at Wk 10
			PER PROTOCOL	Received oral CS > 30 mg/d or >0.5 mg/kg/d at any time during study
			PER PROTOCOL	Treatment with DMARDS at any time during the study
1661	10	F	PER PROTOCOL	Joint Assessor no longer blinded to clinical status at Wk 12
1663	10	M	PER PROTOCOL	Escaped without a valid reason
1192	15	F	PER PROTOCOL	IA, IM or IV CSS within 28 days of baseline visit
1701	15	F	PER PROTOCOL	Ediary temperature not recorded on 4 or> of 7 days preceding Wk 12

Source: WA18221 CSR, slec01 pages 257-9.

Of the 112 randomized patients, 17 (15.2%) were excluded from the PP population (Table 35). Patients could have had more than one reason for exclusion from the PP population and there were no noteworthy differences between the groups with respect to the proportion of patients excluded or the reasons for exclusion. The most common reasons for exclusion were receiving oral CS > 30 mg/day or > 0.5 mg/kg/day at any time during the 12 weeks in study Part I or a missed IV infusion of study medication at Week 10. A line listing of patients excluded from WA18221 analysis is included in Table 36.

Patient Disposition, Baseline Demographics, Baseline Disease Characteristics

These have been discussed section 6.1.3 Demographics, and section 6.1.4 Patient Disposition, above. The reader is referred to sections 6.1.3 and 6.1.4 for further details.

Efficacy Results

Refer to Section 6. Integrated Review of Efficacy, which contains the individual study
results for WA18221 with additional supportive data from Chugai sJIA studies.

Safety Results

Refer to section 7 Integrated Review of Safety