Assessment report for

RoActemra

International Nonproprietary Name: Tocilizumab

Procedure No. Type II variation EMEA/H/C/955/II/15

Assessment Report as adopted by the CHMP with

all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Tocilizumab (TCZ), the active substance of RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Systemic idiopathic juvenile arthritis (sJIA) is a subtype of juvenile idiopathic arthritis characterised by systemic manifestations of disease in addition to arthritis. It occurs at all ages with some predilection for children less than 5 years of age. Currently JIA is diagnosed with a minimum disease duration of 6 weeks. There are no pathognomonic features for sJAI but diagnosis is usually made after 2 weeks of daily high fever spikes, transient rash, importantly development of arthritis may lag behind by months. Other manifestations of disease are hepatosplenomegaly, lymphadenopathy and serositis. sJIA accounts for 10-20% of all JIA cases.

Important complications of the disease are disability, osteoporosis, growth retardation, secondary amyloidosis and anaemia. A life-threatening complication occurring in about 5% of cases is the so-called macrophage-activation syndrome (MAS) which is an overwhelming systemic inflammatory reaction.

About 50% of patients develop an unremitting course; about a quarter of patients develop severe arthritis with significant disability.

Currently there are no authorized medicinal products indicated in the treatment of sJIA in the European Union. Treatment for sJIA is mainly empirical, there are few controlled trials. Treatment options encompass non-steroidal anti-inflammatory drugs but are usually not sufficient and high dose glucocorticoids are added initially and for exacerbations. Because of the known side effects of glucocorticoid treatment methotrexate is recommended as disease modifying therapy although it appears to be less effective than in oligoarticular and polyarticular JIA. Azathioprine is less commonly used. Cyclosporine A and thalidomide have also been reported to be efficacious in patients with ongoing disease activity despite treatment with glucocorticoids and MTX. Etanercept is approved for polyarticular JIA but appears to have markedly lower efficacy in sJIA it and therefore has no indication in sJIA (registry study, Ann Rheum Dis. 2004;63:1638–44). Adalimumab is approved for polyarticular JIA and used off-label for sJIA, Anakinra is currently used off-label and uncontrolled studies support its use, clinical studies are ongoing for canakinumab. Patients with refractory disease have been subjected to autologous stem cell transplantation.

The initially applied wording for extension of indication reads as follows:

"RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with one or more NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy or in combination with MTX".

Furthermore, the MAH requested consideration of this application under Article 14(11) of Regulation (EC) No 726/2004 and submitted a justification that the application concerns a new therapeutic indication which is claimed to bring a significant clinical benefit in comparison with existing therapies.

The applicant received Scientific Advice from the CHMP on 24 May 2007. The Scientific Advice pertained to clinical aspects of the dossier.

The main study supporting this application (WA18221), which was designed to evaluate the efficacy and safety of tocilizumab in paediatric patients with active systemic juvenile idiopathic arthritis, was subject to an agreed Paediatric Investigation Plan.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006 as amended, the application included an EMA decision (P/71/2010) on the agreement of a paediatric investigation plan (PIP) with a deferral.

The PIP is not yet completed.

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

1.2. Non-clinical aspects

Introduction

No additional non-clinical pharmacology investigations have been performed to support the use of tocilizumab in the paediatric indication of sJIA. Additional information elaborated in the context of a toxicity study in juvenile mice with the rat IgG surrogate antibody to tocilizumab, MR16-1 was provided.

This nonclinical study in juvenile animals was conducted in accordance with GLP.

Toxicology

Dose Finding Study for Juvenile Toxicity Study of MR16-1 by Intravenous Administration in Mice (Report No. 1019245)

This study aimed to evaluate an appropriate dosing regimen, in terms of systemic exposure, for a subsequent toxicity study of MR16-1 in juvenile mice. Dosages of 15- (either as a constant dose or preceded by a single loading doses of 50- and 100-mg/kg) and 50-mg/kg (constant dose) were administered intravenously once every three days from postnatal day 22 (up to 7 doses) to 9 male and 9 female Crlj:CD1 (ICR) juvenile mice per dose group. Systemic exposure to MR16-1 and anti-drug antibodies were assessed at 72 hours after the first, third and seventh doses.

In the dose finding study, it was concluded that the dosing regimen for the high dose group for the subsequent main toxicity study of MR16-1 in juvenile mice should be a constant dosing of 50-mg/kg and that for the low dose group should be 15-mg/kg accompanied with a loading dose of 50-mg/kg.

A Toxicity Study to Evaluate the Effects of MR16-1 on Postnatal Development and Growth in Juvenile Mice (Report No. 1019259)

Since tocilizumab does not cross-react with the rodent IL-6 receptor, a juvenile toxicity study was conducted in mice using a murine surrogate antibody for tocilizumab, MR16-1. This juvenile toxicity study focused on immunocompetence, skeletal development and sexual maturation under inhibition of IL-6 signaling.

In this study, dosages of 0, 15- (preceded by a single loading dose of 50-mg/kg) and 50-mg/kg (constant dose) of MR16-1 were administered intravenously once every 3 days from after weaning (postnatal day 22) until postnatal day 79 (11 weeks old and sexually mature) to Crlj:CD1 (ICR)

juvenile mice (12 males and 12 females in the main toxicity and satellite groups); in order to assess the reversibility of any signs of toxicity during a 50-day recovery period 6 males and 6 females in the main recovery and satellite recovery groups were included. Systemic exposure of MR16-1 and anti-drug-antibodies were measured in separate toxicokinetics groups (first, seventh, thirteenth and final dosing, and on days 20 and 50 of recovery) and in satellite group animals at necropsy.

In the 15-mg/kg group which received a single loading dose of 50-mg/kg, MR16-1 concentrations increased gradually after repeated doses in comparison with those after the first dose. The exposure in this group was rather stable without any indication for loss in exposure due to an immune response against MR16-1. The MR16-1 concentration on day 20 of recovery decreased in comparison with those 72 hours after the final dosing. On day 50 of recovery, the concentrations found were below the lower limit of quantification in all samples.

In the 50-mg/kg group, MR16-1 concentrations on day 20 of recovery decreased in comparison with those 72 hours after the final dosing. Two of the three samples from males on day 50 of recovery were BLOQ, and the remainder of samples were close to the BLOQ.

For the satellite groups, MR16-1 concentrations 72 hours after the final dosing and on day 50 of recovery were comparable to those for the toxicokinetics group. There was no difference in exposure levels between sexes.

A summary of toxicokinetic parameters in toxicokinetics group is stated in the below table:

Group	Dose	Sex	Parameters	MR16-1 concentration (µg/mL)	
				First dosing	Final dosing
2	Loading dose 50 mg/kg, Maintenance dose 15 mg/kg	Male	$C_{0.5h}$ [1)]	578 ± 36	683 ± 77
			AUC_{0-72h} [2)]	23437.9	39556.3
		Female	$C_{0.5h}$ [1)]	579 ± 85	626 ± 68
			AUC_{0-72h} [2)]	26769.2	35295.4
3	Loading dose 50 mg/kg, Maintenance dose 50 mg/kg	Male	$C_{0.5h}$ [1)]	599 ± 48	2300 ± 260
			AUC_{0-72h} [2)]	25080.9	123596.3
		Female	$C_{0.5h}$ [1)]	539 ± 121	2790 ± 540
			AUC_{0-72h} [2)]	23772.6	127708.6

In the anti-MR16-1 antibody analysis, none of the samples for the 15- or 50-mg/kg group during dosing period showed positive reactions for anti-MR16-1 antibodies. On day 20 of recovery, 1 of the 3 females in the 15-mg/kg group was positive for anti-MR16-1 antibodies. On day 50 of recovery, 1 of the 6 females for the 15-mg/kg satellite recovery group and 1 of the 6 males for the 50-mg/kg satellite recovery group were positive for anti-MR16-1 antibodies. None of the other samples for the 15- or 50-mg/kg group after the completion of dosing period showed positive reactions for anti-MR16-1 antibodies.

No animal died, and no abnormality was observed in clinical signs in any treatment group during the dosing or recovery period.

No adverse effects were observed in body weight, food consumption, necropsy, organ weights or histopathology in any treatment group during the dosing or recovery period.

With respect to sexual maturation and skeletal development in juvenile animals, there were no adverse effects on the morphological differentiation of external genitalia, estrous cycle, sperm examination, crown-rump length, or skeletal development in any treatment group.

Determinations of lymphocyte subsets revealed some evidence for treatment related changes. In haematology, low monocyte values in females in the 50- and 15-mg/kg groups were observed at the end of dosing period. The values seemed to be within the ranges of physiological changes and the control background data.

Low glucose values were observed in males and females in the 15- and 50-mg/kg groups at the end of dosing and recovery periods. Furthermore, in the 15- and 50-mg/kg groups, high globulin and α2-globulin values, and low β-globulin and A/G values were observed in males and females at the end of dosing periods. In addition, high values in A/G, and low values in α2-globulin were observed in males at end of recovery period in the 50-mg/kg groups. These changes were likely due to the detection of MR16-1, an IgG1 antibody, together with the peak of α2-globulin. It is evident that the presence of such an antibody interferes with the assay format. Therefore, these changes were not considered to indicate toxicity.

In the 15- and 50-mg/kg groups, decreases in CD3e+CD4+CD8a− and CD3e+, and increases in CD45R/B220+ and CD49b/Pan-NK cells+CD3e− were observed in immunophenotyping in peripheral blood in males and females at the end of dosing and recovery periods. In these groups, an increase in CD45R/B220+ in immunophenotyping in spleen was also noted in females at the end of recovery period.

For determination of functionality of NK cells one-third of the spleen was minced, and cell suspension (effector cell) from the spleen was prepared. Functional determination of NK cell activity and immunocompetence (serum IgG and IgM production to KLH) did not yield any recognizable effect of treatment with MR16-1.

Ecotoxicity/environmental risk assessment

In accordance with the CHMP guidance EMEA/CHMP/SWP/4447/00, proteins are exempted because they are unlikely to result in a significant risk to the environment. Tocilizumab, the active ingredient in RoActemra, is a protein (monoclonal antibody). Therefore, an ERA is not provided in this variation application. This is considered acceptable by the CHMP.

Discussion on non-clinical aspects

An additional safety study for assessment of effects in juvenile mice treated intravenously with a murine surrogate antibody for tocilizumab, MR16-1, from weaning until sexual maturity was conducted. The doses used in the study were defined in a dose-finding study.

Anti-drug antibody studies revealed that that there was maximal pharmacological efficacy maintained over the whole study duration at both doses of MR16-1 in this pivotal safety study.

Determinations of lymphocyte subsets revealed some evidence for treatment related changes after end of dosing and at the end of recovery but did not result in any changes on the capacity of the immune system regarding NK cell activity or to mount an IgG or IgM mediated immunization response.

Conclusion on the non-clinical aspects

MR16-1 did not induce any toxicologically meaningful changes on postnatal development and growth, skeletal development, and sexual maturation to juvenile animals. Changes in lymphocyte subsets were

observed under treatment. Further non-clinical studies to address whether these changes will recover are not expected since the MAH demonstrated that the changes did not impact the functional immune response. Overall the results did not yield evidence for a toxicologically impact of IL-6R signalling inhibition on the development of mice treated from weaning until full sexual maturity.

1.3. Clinical aspects

- Tabular overview of clinical studies

This application is based on the data from the following trials:

Study # Phase Location	Study Design	Treatment Dose/Regimen	Duration	Study Status No. of Patients Age range
WA18221 Part I	randomized, double blind, placebo-controlled, parallel group	12 mg/kg <30 kg and 8 mg/kg ≥30 kg	12 weeks	n=112, 75 TCZ, Ages 2-17
WA18221 Part II	Single arm, open label	12 mg/kg <30 kg and 8 mg/kg ≥30 kg	92 weeks	Ongoing, LTE cut at 10 May 2010
LRO320 Phase II EU	Multi-center, open-label, single dose, cohort dose escalation	TCZ: 2, 4, or 8 mg/kg, 6 pts per cohort (3/ age group) Two age groups 2-5Y/O, 6-18 Y/O per dose level	Single dose	18 completed 18 dosed 0 withdrawn Ages 2 - 17 yrs
MRA011JP Phase II Japan	Single-center, open-label, intra-patient dose escalation/ titration study with extension phase	TCZ: 2 mg/kg q2wks x 3, then dose adjustment based on objective to normalize CRP response; 4 mg/kg q2wks, 8 mg/kg q2wks	6-14 wks (dose escalation) followed by >1-year extension phase	10 completed 11 dosed 1 withdrawn Ages 3 - 18 yrs
MRA316JP Phase III Japan	Multi-center, double-blind, randomized, placebo-controlled, withdrawal study	TCZ: 8 mg/kg q2wks x 3 (open phase) followed by 8 mg/kg or placebo q2wks x 6 (double-blind withdrawal phase)	6 wks followed by 12 wk DB withdrawal phase	50 completed 56 dosed 6 withdrawn Ages 2 - 19 yrs
MRA317JP Phase III Long Term Extension Japan	Multi-center, open-label extension for MRA011JP and MRA316JP	TCZ 8 mg/kg q2wks	Study continued until commercially available in Japan ~5 years	56 completed 60 dosed (10 from MRA011JP and 50 from MRA316JP) 2 withdrawn
MRA324JP Phase III Expanded Access Program Japan	Multi-center, open-label, expanded access study (refractory sJIA pts)	TCZ 8 mg/kg q2wks, dosing interval can be shortened to 1 week	Study continued until commercially available in Japan ~2 years	74 completed 82 dosed Ages 2 - 34 yrs including 11 pts with ≥20 years of age 8 withdrawn

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.
The MAH has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

1.3.1. Pharmacokinetics

Paediatric PK data derive from the studies WA18221, LRO320, MRA011JP and MRA316JP.

In study WA18221 blood samples for PK (TCZ serum concentrations) and PD (IL-6, sIL-6R) were collected at pre-dose and post-dose (end of infusion) on Day 1 and at Weeks 2, 4 and 10, pre-dose at Weeks 6, 8, and 12 and at anytime during the week at Weeks 1 and 11. Anti-TCZ antibodies were collected at Baseline (pre-dose on Day 1) and at Week 12.

All patients who had at least one quantifiable TCZ serum concentration were included in the PK analysis. The observed TCZ concentrations over time were summarized using summary statistics.

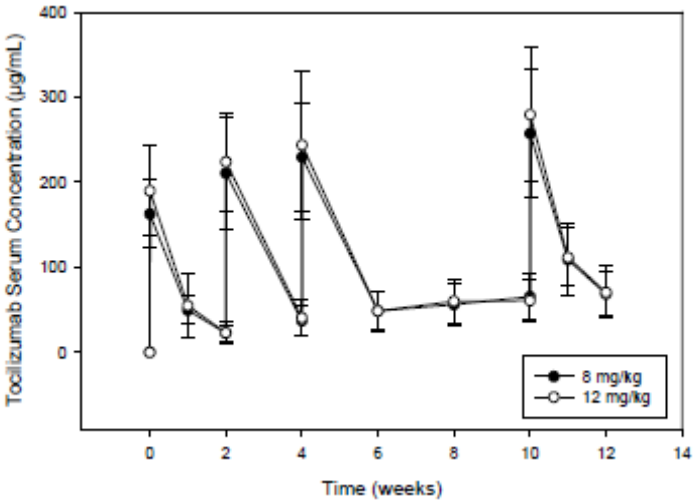
Nonlinear mixed effects modelling (using NOMMEM version 6) was used to analyze the serum TCZ concentration-time data collected over 12 weeks of treatment. The primary PK parameters were clearances and volumes of distribution. Systemic exposure, defined as the area under the serum concentration-time profile (AUC_{2weeks} at Week 12), Cmax concentration post infusion and Cmin concentration at end of a dosing interval (at Week 12) were estimated for all patients who had provided samples.

For all patients, the pos-hoc PK estimated exposure parameters (AUC_{2weeks}, Cmin and Cmax) at Week 12 were summarized using descriptive statistics. These exposure parameters were also summarized by sex, age category (2-5 years, 6-12 years, 13-18 years), treatment group (8 mg/kg, 12 mg/kg), four exposure quartiles (Q1, Q2, Q3, Q4), JIA ACR30/50/70/90 response status at Week 12, patients with fever at baseline but free of fever at Week 12, and anti-TCZ antibody assay result (positive, negative). Quartiles were defined as those patients falling within 0 - ≤ 25%, >25 - ≤50%, >50 - ≤75%, and >75-100% of exposures.

Results

All PK and PK-PD outputs were based on the PK population (n=75) and all PD outputs were based on the Safety population (n=112). All study treatment groups were summarized in PD outputs. However, in PK, PK-PD, PK-efficacy and PK safety outputs, only those patients randomized to TCZ were presented as they were exposed to active treatment (n=75).

The mean (± SD) serum tocilizumab concentration time profile by treatment group in study WA18221 is shown in the below figure:



Posthoc estimated PK exposures (AUC_{2weeks}, Cmin and Cmax) by respective exposure quartiles are displayed in Table 1.

Table 1 Summary of tocilizumab PK parameters at week 12 for all patients

Parameter		Quartile 1 N=19	Quartile 2 N=19	Quartile 3 N=19	Quartile 4 N=18
C_{max}, µg/mL	Mean ±SD CV%	174 ±25.7 14.8	228 ±10.5 4.6	262 ±12.0 4.6	319 ±35.2 11.0
C_{min}, µg/mL	Mean ±SD CV%	30.1 ±8.1 26.9	48.9 ±4.0 8.2	63.0 ±5.1 8.1	89.9 ±13.8 15.4
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD CV%	849 ±147 17.3	1178 ±68.4 5.8	1445 ±105 7.3	1925 ±187 9.7

Because of the twice as frequent dosing compared to adults higher exposure is reached. The exposure is approximately twice as high as in adults as regards AUCss and the Cmin is about 7fold higher (adult 9.7 µg/ml, 69.5 µg/ml). PK/PD/efficacy analyses indicate that the current dose is in the plateau phase of the dose/efficacy curve.

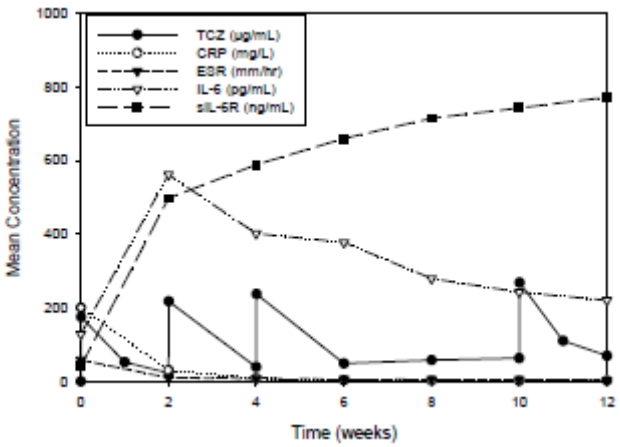
Pharmacodynamics

PK-PD Relationships

Quantitative immunoglobulin levels, serum IL-6, sIL-6R, human serum CRP, ESR, and SAA from WA18221 were summarized graphically and descriptively.

The relationship between TCZ serum concentration and PD markers over 12 weeks of treatment for all who received TCZ treatment is displayed in the following figure:

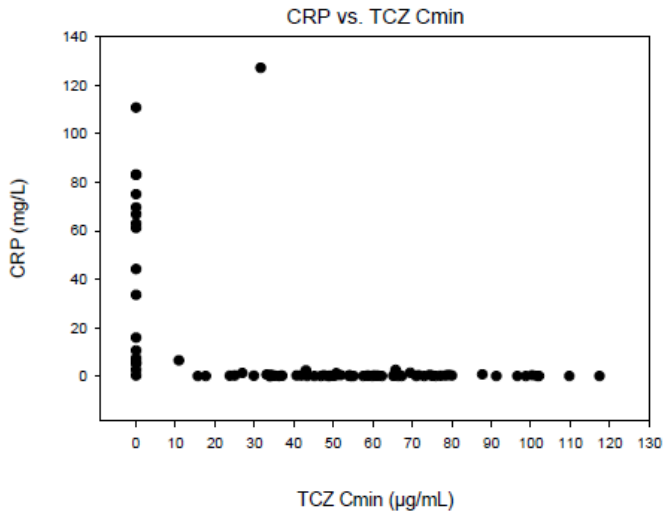
Relationship of tocilizumab PK and mean PD markers in all patients who received tocilizumab



Following administration of TCZ, the mean concentration of IL-6 increased rapidly and subsequently declined gradually trending toward baseline. Mean sIL-6R increased rapidly at Week 2 and continued to increase, approaching a plateau through Week 12 as the TCZ concentration approached a steady state. Markers of inflammation (ESR and CRP) rapidly declined by Week 2 following administration of TCZ and persisted at low levels through Week 12.

Scatter plots of TCZ Cmin (posthoc estimated Cmin at Week 12) values and CRP are shown in the following figure:

Relationship of tocilizumab Cmin and CRP (WA18221, N = 75)



CRP was low when the Cmin was above 10 µg/mL. There was no appreciable relationship between the TCZ Cmin value and IL-6 concentrations, but IL-6 concentrations were generally low as long as the TCZ concentration was above 20 µg/mL, except for a few outliers. In contrast, sIL-6R was elevated when the Cmin value was above 10 µg/mL.

PK-Efficacy Relationship

A summary of percentage of patients achieving JIA ACR30 and absence of fever response status at Week 12 by exposure quartiles is displayed in the Table 2:

Table 2 Summary of Percentage of Patients Achieving JIA ACR30 and Absence of Fever Response Status at Week 12 by Exposure Quartiles

Parameter		Q1	Q2	Q3	Q4
C_{max}	N Responders (%)	19 15 (78.9)	19 17 (89.5)	19 16 (84.2)	18 16 (88.9)
C_{min}	N Responders (%)	19 16 (84.2)	19 17 (89.5)	19 15 (78.9)	18 16 (88.9)
$AUC_{2\ weeks}$	N Responders (%)	19 16 (84.2)	19 17 (89.5)	19 16 (84.2)	18 15 (83.3)

Percentages are based on n in each quartile.
Responders are patients who had a JIA ACR30 response at Week 12 and absence of fever (temperatures <37.5C) in the 7 days preceding the Week 12 assessment day.

There was no clear trend toward higher PK exposures (AUC_{2weeks}, Cmin, and Cmax) in responders compared to non-responders considering the considerable overlap. There was a similar proportion of patients within each exposure quartile who achieved the primary endpoint, ACR30 response and absence of fever at week 12.

PK-Safety Relationships

A summary of PK exposures (AUC2weeks, Cmin, and Cmax) by the worst Neutrophil CTC Grade experienced up to Week 12 for all patients is displayed in the following Table 3:

Table 3 Summary of TCZ PK Exposures by the Worst Neutrophil CTC Grade Experienced up to Week 12 for All Patients

Parameter		Grade 0 N=59	Grade 1 N=0	Grade 2 N=10	Grade 3 N=5	Grade 4 N=0
C_{max}, µg/mL	Mean ±SD	243 ±62.7	-	252 ±32.8	257 ±24.8	-
	CV%	25.8	-	12.0	9.6	-
C_{min}, µg/mL	Mean ±SD	56.2 ±24.6	-	57.0 ±14.5	75.8 ±20.2	-
	CV%	43.8	-	25.4	26.6	-
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD	1313 ±435	-	1357 ±304	1672 ±272	-
	CV%	33.1	-	22.4	16.3	-

No patients had reported neutrophil CTC grade 4. Mean exposures ($AUC_{2\ weeks}$, Cmin and Cmax) were similar between patients with grades 0 (n=59 across treatment groups) and 2 (n=10 across treatment groups). The mean exposures for the 5 patients with CTC grade 3 were somewhat higher at 1672 µg x day/mL, 75.8 µg/mL, and 257 µg/mL compared with CTC grade 0 at 1313 µg x day/mL, 56.2 µg/mL, and 243 µg/mL, for AUC2weeks, Cmin and Cmax, respectively.

There is no clear exposure effect relationship. Further analysis of the data indicates that tocilizumab exposure is in the plateau phase of the exposure-response relationship. It is unclear at present if this higher exposure is required for therapeutic efficacy.

Data from the trial MRA316JP (see efficacy section) seemed to indicate that JIA ACR 50 response was lower in patients with lower body weight, therefore the alternative dosing for children <30 kg was developed. Of note MRA316JP evaluated efficacy at week 6, steady state was not reached at this timepoint. Data from the WA18221 indicate that exposure is considerably higher in children compared to adults therefore the initial assumptions were not confirmed.

Discussion on clinical pharmacology

Data from trials LRO320, MRA011JP, MRA316JP were used to model and justify the doses used for the pivotal trial. Modelling led to the selection of the 12 mg/kg dose for patients <30 kg and the 8 mg/kg dose for patients ≥30 kg.

The chosen doses in the two groups defined by weight show comparable exposure and the body-weight dosing regimen is acceptable. The higher dosing frequency leads to a two fold higher AUC and a 7 fold higher Cmin compared to the adult RA population.

PD markers (CRP, ESR, SAA) indicate that the dosing result in an effect that is in the plateau phase of the dose-effect curve. The lack of a clear correlation of neutrophil count with exposure may simply be due to the short study duration and the low patient number treated but could also indicate that even the lowest exposure has the full effect. In the adult population this relationship is rather clear and there is no good reason to believe that this is different in children. In addition baseline values for neutrophils were higher in the paediatric population; even a considerable drop would lead to normalisation. As corticosteroids also induce neutrophilia it is possible that the neutropenia will become apparent in the long term study if further reduction of corticosteroid dose is possible.

The MAH was requested to further justify the proposed posology and discuss further plans to investigate lower doses in the initial therapy phase. The MAH explained in detail the data which lead to the more frequent dosing regimen of 2 weekly doses of 8 mg/kg in the sJIA population. The rationale is comprehensible and was based on the assumption of a higher CL in children estimated from data of a small number of children. However, the predicted 4-5 fold higher clearance for the sJIA population was not confirmed in the WA18221 study. The proposed SmPC section 5.2 a level of 0.14 ml/h/kg is given as linear CL in the sJIA population. This agrees to the CL in RA adults of 12.5 ml/h which corresponds

to 0.18 ml/h/kg in a 70 kg adult. Thus, the higher TCZ levels in children compared to adults are due the doubling of the dosing frequency and not due to 'different PK properties in the two diseases'.

From the PK/PD evaluation it is clear that PD markers respond rapidly i.e. already after the first dose if viewed on the population level, as demonstrated and argued by the MAH because of inter-individual variability of PK this will not always be the case for the individual. However, given that the majority show an immediate PD response one would therefore conclude that AUC/concentration that is achieved after first dosing is sufficient. This would imply that for continued dosing a lower dose would likely be sufficient, as most antibodies reach steady state only after a prolonged time (caused by long half-life and infrequent dosing). This would argue for a first dose/maintenance dosing concept for the treatment.

The CHMP acknowledged the proposed dose regimen as reasonable for treatment initiation given the favourable benefit/risk appraisal based on the available data in this severe and rare condition. Importantly however, the MAH will investigate lower doses for maintenance of therapy, which will be followed-up post-authorisation. In this context the MAH has presented a detailed and comprehensive description of the amendment of the WA18221 part III protocol which includes the investigation of the feasibility of less frequent dosing of TCZ in the sJIA population. The proposed alternative flexible dosing schedule is considered appropriate to be explored. The MAH will provide interim results with PSURs to monitor the appropriateness of the treatment recommendations, and to submit the clinical study report by February 2015.

The MAH will perform a study to investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients as detailed in the RMP. This study will collect data on efficacy, PD as well as safety upon reduction of dose in patients that have achieved a clinical response (defined by JIA-ACR) but are experiencing above mentioned AE (see safety section).

As the assay for the detection of anti-drug antibodies is sensitive to presence of tocilizumab this higher drug concentrations could lead to an underestimation of anti-drug antibodies in children compared to adults.

Conclusions on clinical pharmacology

Pharmacokinetic behaviour in children appears to be comparable to adults. The finding of the most appropriate dose for this population is largely dependant on modelling; children have a higher exposure compared to adults. The proposed dosing regimen is considered acceptable based on the available data. It remains to be demonstrated in long-term clinical trials if the high exposure obtained is required for the maintenance of pharmacodynamic effect and ultimately efficacy. The MAH has presented a detailed plan for further investigating a reduction of dose once the desired therapeutic response has been achieved; the approach as detailed in the RMP (WA18221 part III protocol) is endorsed by the CHMP.

1.3.2. Clinical efficacy

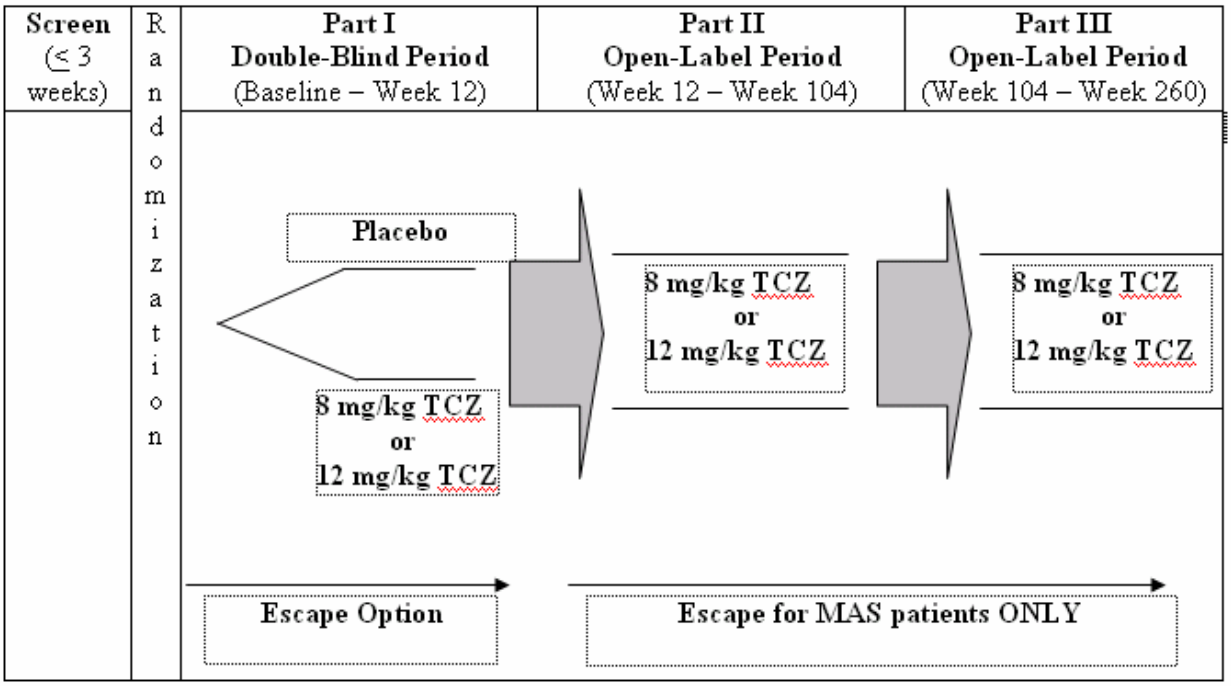
Evidence for the efficacy of TCZ in patients with sJIA is based on the ongoing pivotal Phase III study, WA18221, which includes data from the first 12 weeks of treatment (Part 1). Supportive information comes from a controlled Phase III study, MRA316JP. Long-term efficacy data are also available from the extension study MRA317JP (patients enrolled from studies MRA011JP and MRA316JP) and the expanded access study (MRA324JP).

Main studies

Pivotal study WA18221: 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of tocilizumab in patients with active systemic juvenile idiopathic arthritis (sJIA); with a 92-week single arm open-label extension to examine the long term use of tocilizumab, followed by a 3 year open label continuation of the study to examine the long term use of tocilizumab.

Methods

WA18221 is a pivotal Phase III, randomized, double-blind, placebo controlled, parallel group, multi-center, 2-arm study in three parts in paediatric patients with active sJIA who have had an inadequate clinical response to NSAIDs and corticosteroids due to toxicity or lack of efficacy. The first part of the study was designed to evaluate the efficacy and safety of TCZ for 12 weeks compared to placebo. Patients who completed 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 (8 mg/kg or 12 mg/kg depending on weight). Patients who entered escape during Part I and who were benefiting from receiving TCZ were also able to enter Part II.



The protocol offered an escape option in the placebo controlled phase. Criteria for entering escape were the following:

- 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

Persistent or worsening disease from baseline constitutes an acceptable reason for offering escape in this ill population.

Study Participants

The key inclusion criteria were:

- Age 2 up to and including 17 years at screening into trial;
- Systemic Juvenile Idiopathic Arthritis according to ILAR classification (2001);
- 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.
- 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.
- hsCRP >4.3 mg/L (1.5 x ULN (ULN= 0.28 mg/dl));
- Recovered from any symptomatic serositis for at least one month prior to the screening visit, and requiring dose of corticosteroids ≤ 30 mg/day or 0.5 mg/kg/day, whichever is less, at baseline
- 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/m2 for at least 8 weeks prior to the baseline visit, together with either folic acid or folinic acid according to local standard of care.
- Not currently receiving oral corticosteroids, or taking oral corticosteroids 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;
- 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;

Concomitant treatment with NSAIDs, MTX and corticosteroids was allowed, other DMARDs (leflunomide, cyclophosphamide, etoposide, hydroxychloroquine, gold, azathioprine, sulfasalazine, cyclosporine, thalidomide, penicillamine) and biologics (etanercept, anakinra, abatacept, infliximab, adalimumab) were not permitted.

Treatments

In the TCZ group, patients <30 kg received a dose of 12 mg/kg and patients ≥30 kg 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 kg to/from ≥30 kg).

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

Objectives

Part I

1. To assess the efficacy of TCZ versus placebo in combination with stable ongoing therapy at 12 weeks, with regard to signs and symptoms in sJIA patients with persistent activity and an inadequate response to NSAIDs and systemic CSs;

2. To evaluate the short term safety of TCZ versus placebo in combination with stable ongoing therapy at 12 weeks, with regard to adverse events (AEs) and laboratory assessments in patients with sJIA with persistent activity and an inadequate response to NSAIDs and CSs.

Part II

1. To evaluate the safety of tocilizumab in chronic administration;

2. To assess the effect of tocilizumab to enable the reduction or elimination of corticosteroids.

Part III

1. To assess the long-term safety of 8 mg/kg tocilizumab in children >30 kg and 12 mg/kg tocilizumab in children <30 kg with regard to adverse events and laboratory result abnormalities;

Outcomes/endpoints

Primary endpoint

Proportion of patients with a JIA ACR30 response and absence of fever at Week 12. Absence of fever was defined as no temperature recording ≥37.5° C in the preceding seven days. Presence of fever defined as any recording ≥37.5° C in the preceding seven days.

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 who have 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 of overall well-being VAS at Week 12;

10. The proportion of patients with anaemia at Baseline who increase Hgb by ≥10 g/L at Week 12;

11. The proportion of patients with anaemia at Baseline who increase Hgb by ≥10 g/L at Week 6;

12. The proportion of patients with rash characteristic of sJIA at Baseline who are free of rash at Week 12;

13. The CFB in the pain VAS at Week 12;

14. The proportion of patients with a minimally important improvement in the CHAQ-DI by Week 12;

15. The proportion of patients with JIA ACR30 response at Week 12 adjusted for oral CS dose modifications;

16. The proportion of patients receiving oral CSs with a JIA ACR70 response at Week 6 or Week 8 who then reduce their oral CS dose by at least 20% without subsequent JIA ACR30 flare or occurrence of systemic symptoms to Week 12;

17. The proportion of patients with JIA ACR90 response at Week 12;

18. The proportion of patients with thrombocytosis at Baseline who have a normal platelet count at Week 12;

19. The proportion of patients with leucocytosis at Baseline who have a normal total WBC count at Week 12;

20. The proportion of patients with anemia at Baseline who have normal Hgb at Week 12;

21. The percentage CFB in number of joints with active arthritis at Week 12;

22. The percentage CFB in number of joints with limitation of movement at Week 12.

Sample size

Based on literature data, a JIA ACR30 response at Week 12 of 70% in patients on TCZ and of 40% for patients on placebo was assumed for sample size calculation. It was calculated that about 108 patients (72 TCZ, 36 placebo) would provide approximately 80% power to detect such a treatment difference between both treatments using a two-sided chi-square test with α=0.05.

The sample size calculation was considered as acceptable by the CHMP.

Randomisation

Patients were randomized 2:1 to receive either TCZ or placebo respectively. Randomisation was stratified by body weight, disease duration, background CS dose and background MTX use.

Methods for randomisation were considered as acceptable by the CHMP.

Blinding (masking)

This is double blind study.

Statistical methods

Dichotomized variables (e.g. responder) were compared between TCZ and placebo by means of a Cochran-Mantel-Haenszel test. In case of responder analyses, patients who withdrew or escaped were classed as non-responders. To compare TCZ versus placebo with respect to continuous variables, analysis of variance was used. All analyses models accounted for the stratification factors at randomisation. Comparison between each of the TCZ groups and placebo were done descriptively only.

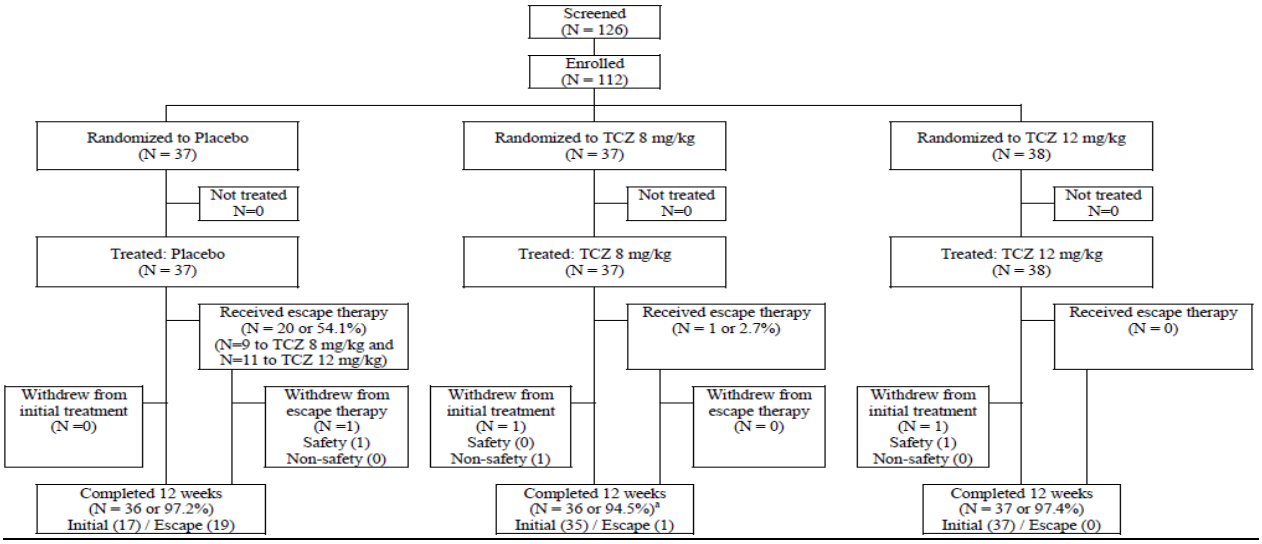
Statistical tests were decided for α = 0.05 (2-sided). To control the Type I error, secondary endpoints were hierarchically ordered and were tested in a pre-defined sequential order. If the sequence was broken, no confirmatory claims could be based on the endpoints that had a rank lower than that endpoint whose null hypothesis was the first that could not be rejected. Treatment effects were described by point estimates including the corresponding 95% confidence intervals.

Various patient baseline characteristics were used to define subgroups for exploratory subgroup analyses (e.g. sex, age, ethnicity, region, number of joints with active arthritis, ESR etc).

In general statistical methods applied were considered as acceptable by the CHMP.

Results

Participant flow



Recruitment

A total of 112 patients were enrolled at 43 centers in 17 countries including Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Germany, United Kingdom, Greece, Italy, Mexico, Netherlands, Norway, Poland, Slovakia, Spain, and United States.

The first patient was screened on 9 May 2008, the last patient completed week 12 assessment on 2 September 2009.

Conduct of the study

The protocol was amended once; all patients had been recruited and completed week 6 assessments before the amendment was put into place.

The majority of changes were clarifications and are considered uncritical. The inclusion criteria were changed even though all patients had already been included. Thus the inclusion criteria of protocol version A define the study population and this may impact external validity.

Baseline data

The demographic characteristics at Baseline in the placebo group and the all TCZ group were similar. In each treatment group, patients were evenly split between male and female patients and they were predominately Caucasian. As expected as a result of the two different doses < or ≥BW 30 kg, the mean age, BW, height, and body surface area (BSA) were higher in the TCZ 8 mg/kg group in comparison to the TCZ 12 mg/kg group. However, these characteristics were similar between the all TCZ group and the placebo group.

Demographic characteristics (ITT population)

	Placebo 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%)
n	37	37	38	75
Race				
AMERICAN INDIAN OR ALASKA NATIVE	2 (5%)	-	-	-
BLACK	-	1 (3%)	-	1 (1%)
OTHER	3 (8%)	1 (3%)	6 (16%)	7 (9%)
WHITE	32 (86%)	35 (95%)	32 (84%)	67 (89%)
n	37	37	38	75
Age in years				
Mean	9.1	13.5	6.6	10.0
SD	4.43	2.86	3.30	4.64
SEM	0.73	0.47	0.54	0.54
Median	9.0	14.0	6.0	10.0
Min-Max	2 - 17	7 - 17	2 - 16	2 - 17
n	37	37	38	75
Weight in kg				
Mean	31.68	49.71	20.07	34.69
SD	16.750	20.077	5.930	20.888
SEM	2.754	3.301	0.962	2.412
Median	28.00	42.30	18.85	29.70
Min-Max	10.1 - 74.2	30.6 - 112.7	10.0 - 29.7	10.0 - 112.7
n	37	37	38	75
Height in cm				
Mean	121.28	145.13	108.08	126.36
SD	20.392	16.327	13.932	23.971
SEM	3.352	2.684	2.260	2.768
Median	121.70	142.00	105.60	125.10
Min-Max	78.8 - 160.6	113.0 - 174.0	76.5 - 133.6	76.5 - 174.0
n	37	37	38	75

sJIA Disease Characteristics

sJIA disease characteristics at baseline included fever and rash status, previous use of DMARDs, previous use of biologics, CRP, and articular and extraarticular damage. The disease characteristics between the placebo and the TCZ group were similar except for a higher proportion of patients with rash (in the 14 days prior to Baseline) in the placebo group (48.6%) compared with the all TCZ group (29.3%). Baseline CRP was lower in the placebo group (mean 95.6 mg/L and median 77.2 mg/L) in comparison with the all TCZ group (mean 200.4 mg/L and median 115.6 mg/L). However, three patients including two in the TCZ 8 mg/kg (1651 and 1373) and one in the TCZ 12 mg/kg group (1372) had very high CRP values that distorted the mean/median summary statistics.

Fever, an important systemic symptom in sJIA, was present (in the 7 days prior to Baseline) in approximately 50% of patients. As expected as a result of the two different doses < or ≥ BW 30 kg, the mean number of previous DMARDs and biologics, and Tanner Stage were higher in the TCZ 8 mg/kg group in comparison to the TCZ 12 mg/kg group. However, these characteristics were similar between the all TCZ group and the placebo group (Table 4).

Table 4 Summary of sJIA Disease Characteristics at Baseline by Trial Treatment (ITT Population)

stdm11_sjia_itt Summary of sJIA Disease Characteristics at Baseline by Trial Treatment (ITT Population)
Protocol(s): WA18221 (B18221A)
Analysis: INTENT TO TREAT Center: ALL CENTERS

	Placebo N = 37	TCZ 8 mg/kg N = 37	TCZ 12 mg/kg N = 38	All TCZ N = 75
Fever Status (Last 7 Days)				
Absent	17 (46%)	25 (68%)	18 (47%)	43 (57%)
Present	20 (54%)	12 (32%)	20 (53%)	32 (43%)
n	37	37	38	75
Fever Status (Last 14 Days)				
Free	13 (35%)	22 (59%)	12 (32%)	34 (45%)
Present	24 (65%)	15 (41%)	26 (68%)	41 (55%)
n	37	37	38	75
Rash Status				
Free	19 (51%)	28 (76%)	25 (66%)	53 (71%)
Present	18 (49%)	8 (22%)	13 (34%)	21 (28%)
Present (M)	-	1 (3%)	-	1 (1%)
n	37	37	38	75
No. of Previous DMARDs				
Mean	1.4	1.6	1.0	1.3
SD	1.42	1.17	0.88	1.07
SEM	0.23	0.19	0.14	0.12
Median	1.0	1.0	1.0	1.0
Min-Max	0 - 5	0 - 4	0 - 3	0 - 4
n	37	37	38	75
No. of Previous DMARDs Category				
0	12 (32%)	8 (22%)	12 (32%)	20 (27%)
1	11 (30%)	11 (30%)	18 (47%)	29 (39%)
2	9 (24%)	8 (22%)	5 (13%)	13 (17%)
>=3	5 (14%)	10 (27%)	3 (8%)	13 (17%)
n	37	37	38	75

	Placebo N = 37	TCZ 8 mg/kg N = 37	TCZ 12 mg/kg N = 38	All TCZ N = 75
No. of Previous Biologics				
Mean	1.6	2.5	1.4	1.9
SD	1.26	1.48	1.13	1.41
SEM	0.21	0.24	0.18	0.16
Median	1.0	2.0	1.5	2.0
Min-Max	0 - 5	0 - 6	0 - 4	0 - 6
n	37	37	38	75
No. of 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%)
n	37	37	38	75
CRP (mg/L)				
Mean	95.58	232.23	169.32	200.36
SD	68.683	534.876	269.008	419.959
SEM	11.291	87.933	43.639	48.493
Median	77.22	95.19	123.22	115.57
Min-Max	1.9 - 302.2	8.7 - 2524.4	5.4 - 1704.9	5.4 - 2524.4
n	37	37	38	75
JADI-A (Articular Damage) (0-72)				
Mean	5.0	5.3	5.0	5.1
SD	5.63	7.64	8.33	7.95
SEM	0.94	1.27	1.35	0.92
Median	3.0	3.5	2.0	2.5
Min-Max	0 - 21	0 - 37	0 - 45	0 - 45
n	36	36	38	74
JADI-E (Extraarticular Damage) (0-17)				
Mean	1.7	1.4	1.4	1.4
SD	1.69	1.81	2.01	1.90
SEM	0.28	0.30	0.33	0.22
Median	1.0	1.0	1.0	1.0
Min-Max	0 - 5	0 - 8	0 - 10	0 - 10
n	36	36	38	74
Tanner Stage (1-5)				
Mean	1.5	3.0	1.1	2.0
SD	1.04	1.52	0.23	1.45
SEM	0.17	0.25	0.04	0.17
Median	1.0	3.0	1.0	1.0
Min-Max	1 - 5	1 - 5	1 - 2	1 - 5
n	37	37	37	74

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Fever status: Present = temperature >=37.5 C in past 7/14 days. Present(M) = fever assumed due to missing diary data. Absent = no temperature >=37.5 C in past 7 days. Free = no temperature >=37.5 C in past 14 days.
Rash status: Present = sJIA rash in past 14 days. Present(M) = sJIA rash assumed due to missing diary data. Free = no sJIA rash in past 14 days.
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JIA ACR Core Set Components

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

Table 5 JIA ACR Core Components at Baseline (ITT Population)

	Placebo 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	16.9	23.5	19.2	21.3
SD	12.91	16.58	15.21	15.94
Median	13.0	19.0	13.5	16.0
Min-Max	5 - 67	5 – 65	3 – 71	3 -71
No. of Joints with Limitation of Movement (0- 67)				
n	37	37	38	75
Mean	17.9	23.4	18.1	20.7
SD	15.90	16.92	14.62	15.91
Median	14.0	20.0	14.5	15.0
Min-Max	1 - 67	0 – 65	0 – 67	0 - 67
Patient/Parent Global Assessment VAS (0-100 mm)				
n	37	37	38	75
Mean	56.3	61.3	59.3	60.3
SD	21.20	22.78	24.98	23.78
Median	52.0	61.0	65.5	65.0
Min-Max	20-100	0-100	8-100	0-100
Physician Global Assessment VAS (0-100 mm)				
n	37	37	38	75
Mean	61.4	68.1	71.1	69.6
SD	21.12	15.10	16.24	15.65
Median	63.0	69.0	71.0	70.0
Min-Max	13-100	17-92	28-100	17-100
CHAQ-DI Score (0-3)				
n	37	37	38	75
Mean	1.6588	1.7095	1.7669	1.7386
SD	0.82319	0.78950	0.79674	0.78833
Median	1.6250	1.8750	1.8750	1.8750
Min-Max	0.000-3.000	0.000-3.000	0.000-3.000	0.000-3.000
ESR (mm/hr)				
n	37	37	38	75
Mean	54.1	50.9	64.1	57.6
SD	35.40	31.71	29.76	31.24
Median	45.0	50.0	69.0	57.0
Min-Max	5-140	5-130	8-130	5-130

n: represents number of patients contributing to summary statistics.

Sources: (page 293 , page 295 , page 297 , page 299 , page 301 , and page 303 , respectively).

Randomization Stratification Variables

The results of the randomisation are provided in Table 6. Across all patients there was an even split (50/50) in the categories of BW, duration of disease and background oral CS dose. However, use of background MTX was high at 70% of the patients.

Table 6 Summary of Randomization Stratification Variables at Baseline by Trial Treatment (ITT Population)

stdm11_stra_itt Summary of Randomization Stratification Variables at Baseline by Trial Treatment (ITT Population)
Protocol(s): WA18221 (B18221A)
Analysis: INTENT TO TREAT Center: ALL CENTERS

	Placebo N = 37	TCZ 8 mg/ N = 37	TCZ 12 mg/kg N = 38	All TCZ N = 75
Weight (kg)				
<30kg	21 (57%)	-	38 (100%)	38 (51%)
>=30kg	16 (43%)	37 (100%)	-	37 (49%)
n	37	37	38	75
Duration of sJIA Disease (years)				
Mean	5.06	6.33	4.03	5.17
SD	4.446	4.412	3.160	3.975
SEM	0.731	0.725	0.513	0.459
Median	3.97	5.05	2.84	3.95
Min-Max	0.6 - 16.1	0.8 - 15.2	0.5 - 13.3	0.5 - 15.2
n	37	37	38	75
Duration of sJIA Disease Category				
<4 years	19 (51%)	16 (43%)	22 (58%)	38 (51%)
>=4 years	18 (49%)	21 (57%)	16 (42%)	37 (49%)
n	37	37	38	75
Background oral CS Dose (mg/kg/day)				
Mean	0.27	0.21	0.36	0.29
SD	0.171	0.152	0.169	0.177
SEM	0.028	0.025	0.027	0.020
Median	0.28	0.19	0.40	0.30
Min-Max	0.0 - 0.5	0.0 - 0.6	0.0 - 0.9	0.0 - 0.9
n	37	37	38	75
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%)
n	37	37	38	75
Background MTX Use				
NO	11 (30%)	16 (43%)	7 (18%)	23 (31%)
YES	26 (70%)	21 (57%)	31 (82%)	52 (69%)
n	37	37	38	75

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
The prednisone equivalent is used in calculation of oral corticosteroid dose.
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Numbers analysed

Analysis was according to the ITT principle. In the placebo group 36/37 patients, in the 8 mg/kg 36/37 patients and in the 12 mg/kg 37/38 patients reached the 12 week endpoint.

Outcomes and estimation

Primary Efficacy Endpoint

Twenty-eight patients treated with TCZ 8 mg/kg and 36 TCZ 12 mg/kg patients met the primary endpoint, the proportions were contrasting with 75.7% and 94.7% of patients in the respective groups (Table 7).

Table 7 Summary and Analysis of the Percentage of Patients with a JIA ACR30 Response and Absence of Fever at Week 12 (ITT Population)

	Placebo (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 (24.3%)	28 (75.7%)	36 (94.7%)	64 (85.3%)
95% C.I.	[10.5; 38.1]	[61.9; 89.5]	[87.6;100.0]	[77.3; 93.3]
Weighted difference vs. Placebo				61.5
95% C.I. of weighted difference				[44.9; 78.1]
p-value				<.0001

Secondary Efficacy Endpoints

All 22 secondary endpoints met the significance level of p ≤0.05.

JIA ACR Responses

The percentages of patients with JIA ACR30/50/70/90 responses at Week 12 are summarized in Table 8.

Table 8 Summary and Analysis of the Percentage of Patients with JIA ACR30/50/70/90 Responses at Week 12 (ITT Population)

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
JIA ACR30 response				
n	37	37	38	75
Responders	9 (24.3%)	31 (83.8%)	37 (97.4%)	68 (90.7%)
95% C.I.	[10.5; 38.1]	[71.9; 95.7]	[92.3;100.0]	[84.1; 97.3]
Weighted difference vs. Placebo				66.8
95% C.I. of weighted difference				[50.7; 82.9]
p-value				<.0001
JIA ACR50 response				
n	37	37	38	75
Responders	4 (10.8%)	29 (78.4%)	35 (92.1%)	64 (85.3%)
95% C.I.	[0.8; 20.8]	[65.1; 91.6]	[83.5;100.0]	[77.3; 93.3]
Weighted difference vs. Placebo				74.0
95% C.I. of weighted difference				[57.9; 90.1]
p-value				<.0001

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
JIA ACR70 response				
n	37	37	38	75
Responders	3 (8.1%)	25 (67.6%)	28 (73.7%)	53 (70.7%)
95% C.I.	[0.0; 16.9]	[52.5; 82.7]	[59.7; 87.7]	[60.4; 81.0]
Weighted difference vs. Placebo				62.9
95% C.I. of weighted difference				[46.1; 79.7]
p-value				<.0001
JIA ACR90 response				
n	37	37	38	75
Responders	2 (5.4%)	13 (35.1%)	15 (39.5%)	28 (37.3%)
95% C.I.	[0.0; 12.7]	[19.8; 50.5]	[23.9; 55.0]	[26.4; 48.3]
Weighted difference vs. Placebo				33.3
95% C.I. of weighted difference				[16.8; 49.7]
p-value				<.0001

JIA ACR Core Components

An analysis of variance of the percentage change from Baseline in the JIA ACR core set components at Week 12 with the all TCZ vs. placebo patients and adjusted for the randomization stratification factors applied at Baseline is shown in (Table 9).

The adjusted mean percentage change from Baseline in number of joints with active arthritis at Week 12 was significantly decreased in the patients treated with TCZ compared to those treated with placebo(TCZ = -70.6% vs placebo = -37.2%; p = 0.0012).

Table 9 Analysis of Variance of Percentage Change from Baseline in the JIA ACR Core Set Components at Week 12 - All TCZ vs. Placebo (ITT Population)

	No. of Active Joints	No. of Joints with Limitation of Movement	Patient/ Parent Global Assessment VAS	Physician Global Assessment VAS	CHAQ-DI Score	ESR
Placebo (N = 37)						
n	17	17	17	17	17	17
Adjusted Mean	-37.2	-22.5	-1.4	-41.1	-10.3	33.6
All TCZ (N = 75)						
n	73	72	73	73	72	73
Adjusted Mean	-70.6	-51.6	-65.8	-69.6	-45.6	-88.2
Difference (a)	-33.4	-29.1	-64.4	-28.5	-35.3	-121.8
95% CI for Difference	[-53.2;-13.6]	[-53.4;-4.9]	[-87.5;-41.3]	[-44.3;-12.8]	[-63.5;-7.1]	[-149.9;-93.7]
p-value	0.0012	0.0192	<.0001	0.0005	0.0148	<.0001

JIA ACR Response and Oral CS Modifications

Of the 31 placebo and 70 TCZ patients receiving oral CSs at Baseline, eight (25.8%) placebo and 48 (68.6%) TCZ patients achieved a JIA ACR70 response at Week 6 or 8 enabling them to reduce their oral CS dose in accordance with the Protocol guidance. One placebo (3.2%) and 17 TCZ (24.3%) patients responded for this endpoint (p=0.0280) (Table 10).

Table 10 Summary and Analysis of the Percentage of Patients Receiving Oral CS with JIA ACR70 Response at Week 6/8 who Reduced Oral CS dose by ≥20% Without Subsequent JIA ACR30 Flare or Occurrence of Systemic Symptoms to Week 12 (ITT Population)

	Placebo (N=31)	TCZ 8 mg/kg (N=34)	TCZ 12 mg/kg (N=36)	All TCZ (N=70)
n	31	34	36	70
Responders	1 (3.2%)	8 (23.5%)	9 (25.0%)	17 (24.3%)
95% C.I.	[0.0; 9.4]	[9.3; 37.8]	[10.9; 39.1]	[14.2; 34.3]
Weighted difference vs. Placebo				20.3
95% C.I. of weighted difference				[2.2; 38.4]
p-value				0.0280

Systemic Features

Fever

Of those patients with fever at Baseline, 35 (85.4%) TCZ patients and five (20.8%) placebo patients were free of fever at Week 12 (p<0.0001).

At Week 12, of those patients who completed study Part I (i.e., did not escape or withdraw) on randomized treatment, fever was present in eight (11.0%) of the TCZ patients in comparison to six (35.3%) of the placebo patients (table 11).

Rash

At Week 12, of those patients who completed study Part I (i.e., did not escape or withdraw) on randomized treatment, rash was present in 12 (16.4%) of the TCZ patients in comparison to three (17.6%) of the placebo patients (table 11).

Table 11 Proportion of Patients Reporting Systemic Symptoms (Fever and Rash) by Visits to Week 12 (ITT Population)

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
Baseline				
n	37	37	38	75
Fever Present	24 (64.9%)	15 (40.5%)	26 (68.4%)	41 (54.7%)
Fever Present (M)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash Present	18 (48.6%)	8 (21.6%)	13 (34.2%)	21 (28.0%)
Rash Present (M)	0 (0.0%)	1 (2.7%)	0 (0.0%)	1 (1.3%)
Week 2				
n	35	37	38	75
Fever Present	19 (54.3%)	6 (16.2%)	10 (26.3%)	16 (21.3%)
Fever Present (M)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (1.3%)
Rash Present	15 (42.9%)	10 (27.0%)	9 (23.7%)	19 (25.3%)
Rash Present (M)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (1.3%)
Week 4				
n	24	37	38	75
Fever Present	8 (33.3%)	5 (13.5%)	6 (15.8%)	11 (14.7%)
Fever Present (M)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash Present	10 (41.7%)	8 (21.6%)	8 (21.1%)	16 (21.3%)
Rash Present (M)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 6				
n	21	36	38	74
Fever Present	7 (33.3%)	2 (5.6%)	3 (7.9%)	5 (6.8%)
Fever Present (M)	0 (0.0%)	1 (2.8%)	1 (2.6%)	2 (2.7%)
Rash Present	5 (23.8%)	6 (16.7%)	10 (26.3%)	16 (21.6%)
Rash Present (M)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (1.4%)
Week 8				
n	19	36	38	74
Fever Present	4 (21.1%)	4 (11.1%)	3 (7.9%)	7 (9.5%)
Fever Present (M)	1 (5.3%)	1 (2.8%)	0 (0.0%)	1 (1.4%)
Rash Present	5 (26.3%)	6 (16.7%)	6 (15.8%)	12 (16.2%)
Rash Present (M)	1 (5.3%)	1 (2.8%)	0 (0.0%)	1 (1.4%)
Week 10				
n	18	36	38	74
Fever Present	5 (27.8%)	4 (11.1%)	2 (5.3%)	6 (8.1%)
Fever Present (M)	1 (5.6%)	1 (2.8%)	1 (2.6%)	2 (2.7%)
Rash Present	2 (11.1%)	9 (25.0%)	12 (31.6%)	21 (28.4%)
Rash Present (M)	1 (5.6%)	1 (2.8%)	0 (0.0%)	1 (1.4%)
Week 12				
n	17	36	37	73
Fever Present	6 (35.3%)	6 (16.7%)	1 (2.7%)	7 (9.6%)
Fever Present (M)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (1.4%)
Rash Present	3 (17.6%)	6 (16.7%)	5 (13.5%)	11 (15.1%)
Rash Present (M)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (1.4%)

Summary of main studies

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12. Summary of Efficacy for trial *WA18221*

A 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of tocilizumab (TCZ) in patients with active systemic juvenile idiopathic arthritis (sJIA); with a 92-week single arm open-label extension to examine the long term use of TCZ, followed by a 3 year open label continuation of the study to examine the long term use of TCZ.		
Study identifier	WA18221	
Design	randomized, double blind, placebo-controlled, parallel group	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks not applicable 3 years
Hypothesis	Superiority	
Treatments groups	Placebo	n=37

	Tocilizumab		8 mg/kg (>30 kg bodyweight) or 12 mg/kg (<30 kg body weight) n=75
Endpoints and definitions	Primary: JIA ACR 30 and absence of fever	JIA ACR30 and no fever	JIA ACR30 improvement is defined as 3 of any 6 core outcome variables improved by at least 30% from the baseline assessments, with no more than 1 of the remaining variables worsened by more than 30% and absence of fever Absence of fever was defined as no diary temperature recording ≥37.5° C in the preceding seven days
	Secondary: JIA ACR50	JIA ACR50	JIA ACR50 improvement is defined as 3 of any 6 core outcome variables improved by at least 50% from the baseline assessments, with no more than 1 of the remaining variables worsened by more than 30%
	Secondary: JIA ACR70	JIA ACR70	JIA ACR70 improvement is defined as 3 of any 6 core outcome variables improved by at least 70% from the baseline assessments, with no more than 1 of the remaining variables worsened by more than 30%

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Placebo	Tocilizmab
	Number of subject	37	75
	JIA ACR30 and no fever (responder rate)	24.3%	85.3%
	95%CI	10.5; 38.1	77.3; 93.3
	JIA ACR50 (responder rate)	10.8%	85.3%
	95%CI	0.8; 20.8	77.3; 93.3
	JIA ACR70 (responder rate) 95%CI	8.1% 0.0; 16.9	70.7% 60.4; 81.0
Effect estimate per comparison	Primary endpoint: JIA ACR 30 and absence of fever	Comparison groups	Placebo, tocilizumab
		Difference between groups	61.5%
		95%CI	44.9; 78.1
		Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors, P-value	<0.0001

	Secondary: JIA ACR50	Comparison groups	Placebo, tocilizumab
		Difference between groups	74.0%
		95%CI	57.9; 90.1
		Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors, P-value	<0.0001
	Secondary: JIA ACR70	Comparison groups	Placebo, tocilizumab
		Difference between groups	62.9%
		95%CI	46.1; 79.7
		Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors, P-value	<0.0001

Supportive studies

MRA011JP "Early Phase II Study of MRA for Systemic Juvenile Idiopathic Arthritis"

MRA011JP was an exploratory phase II study investigating the efficacy and safety of tocilizumab in patients with sJIA that had failed to respond to therapy with cortisone, DMARD or immunosuppressants or in whom treatment could not be continued due to adverse drug reactions. Treatment was administered in 2-weekly intervals. Doses started at 2 mg/kg, when insufficient response with respect to CRP defined as CRP ≥15 mg/L was observed dose could be increased to 4 mg/kg and if necessary to 8 mg/kg. Primary endpoint was course of CRP and ESR, JIA ACR was also investigated.

Eleven patients were included in the study. Eight patients were male and 3 were female. Their age (mean ± SD) was 8.5 ± 4.0 years, age at onset of the underlying disease was 4.4 ± 3.6 years, and the disease duration was 3.5 ± 2.7 years. CRP before the start of treatment was 10.14 ± 9.22 mg/dL, and the ESR was 53.4 ± 24.6 mm/hr. All of the patients had previously received corticosteroids, 9 had received cyclosporine, and 8 had received methotrexate. All of the patients had also received other immunosuppressants previously.

The final tocilizumab dose was 2 mg/kg in 3 patients, 5 patients required a dose increase to 4 mg/kg, and 3 patients required a dose increase to 8 mg/kg. CRP decreased after the first infusion at all doses and remained low throughout the study period. The percentage of patients showing normalization of CRP on the last observation day increased as the dose increased, with 100% of the patients who received a final dose of 8 mg/kg showing normal CRP values.

There were 35 adverse events, and these involved all 11 patients. There were 29 adverse drug reactions, and these involved all 11 patients. By SOC, adverse events and adverse drug reactions involving investigations were the most common in terms of both the number of patients and the number of events. There were 18 such adverse events and 18 such adverse drug reactions each involving 10 patients. By preferred term (PT), there was a relatively high incidence of increased blood cholesterol, decreased blood IgG, limb abscesses, and increased β-N-acetyl-D-glucosaminidase among both adverse events and adverse drug reactions. All AE were mild and none were serious.

MRA316JP "Phase III Study of MRA in Patients with Systemic Juvenile Idiopathic Arthritis"

MRA316JP was a phase III trial investigating the efficacy and safety of tocilizumab in patients aged between 2 and 19 years with sJIA (onset at an age <16 years) with a CRP value ≥1.5 mg/dL at baseline that had failed to respond to therapy with corticosteroids or in whom treatment could not be

continued due to adverse drug reactions. During an open label run-in period of 6 weeks patients received three times a week a dose of 8 mg/kg Tocilizumab at 2 weeks intervals. At the end of the run-in period patients with a CRP <0.5 mg/dL and 30% improvement in the JIA core were randomised to receive in a double-blinded fashion either 8 mg/kg tocilizumab or placebo six times at 2-week intervals for another 12 weeks or withdrawal (whichever was first). Maintained response was the primary endpoint of the double blind withdrawal period.

The study was conducted in Japan in 2004 and 2005. Fifty six patients were included into the open-label part of the study whereof 50 patients completed this study part. 51/56 patients (91.1%, 95%-CI: 80.4% to 97.0%) had a JIA ACR30 response at the end of open-label tocilizumab treatment. CRP and ESR were significantly lowered during the run-in period (p <0.001 each).

Forty four JIA ACR30 responders completing the open-label period continued into the double blind withdrawal period. Treatment assignment was done by means of a dynamic allocation procedure. Twenty one patients were randomised to receive tocilizumab, 23 patients were randomized to receive placebo. One patient was excluded from all efficacy analyses due premature unblinding. Both treatment groups were comparable with respect to their demographic and baseline disease characteristics:

	Placebo (n = 23)	Tocilizumab (n = 20)
Gender		
• Male	8	7
• Female	15	13
Age (mean ± SD)	9.3 ± 4.5 yrs	8.0 ± 4.3 yrs
Age at onset of disease	5.1 ± 3.0 yrs	3.9 ± 2.2 yrs
Disease duration	4.7 ± 4.0 yrs	4.6 ± 3.5 yrs
Baseline ESR	38.7 ± 16.2 mm/hr	43.4 ± 25.0 mm/hr
Baseline CRP	4.94 ± 3.22 mg/dL	5.01 ± 4.31 mg/dL
Use of corticosteroids		
• N	23	20
• mean ± SD	0.46 ± 0.33 mg/kg	0.42 ± 0.27 mg/kg
Pretreatment with		
• cyclosporine	15	14
• MTX	21	16

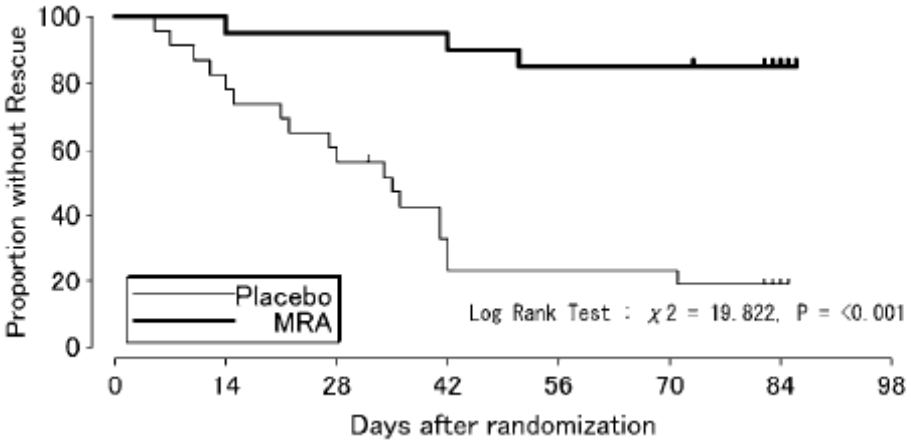
Osteoporosis, cataract and glaucoma, considered to be attributable to corticosteroids, were present in 14, 11 and 8 patients, respectively, from the placebo group and in 13, 7 and 7 patients, respectively, from the tocilizumab group.

The rate of maintained response defined as the percentage of patients who completed the study and to whom neither the withdrawal criteria nor the rescue criteria applied during 12 weeks of the blind period was statistically significantly higher in the tocilizumab group compared to the placebo group:

Treatment	N	Response maintained	Response not maintained	Rate (95%-CI)	p-value
Placebo	23	4	19	17.4% (5.0 – 38.8%)	< 0.001
Toculizumab	20	16	4	80.0% (56.3 – 94.3%)	

A comparison of duration of maintained response between both groups by means of a log-rank test shown in the below figure indicated a statistically significant advantage of toculizumab (p<0.001):

Duration of maintained response



While CRP was below 0.1 mg/dL in all tocilizumab patients during the withdrawal period, an increase in CRP (up to 8.2 mg/dL) was observed in some placebo patients. A similar time pattern was to be observed for ESR: while ESR was stable during the withdrawal period in tocilizumab patients there was a tendency for increased ESR values in placebo patients during this study period.

The study investigated the effect of a dose of 8 mg/kg to maintain a JIA ARC30 response. It was shown that over a 12 weeks period tocilizumab was able to achieve a significantly higher maintenance rate (80%, 95% CI; 56.3 – 94.3%) than placebo (17.4%, 95% CI: 5.0 – 38.8%). Judging this result in comparison to study WA18221 on has to consider several aspects:

- The population of study MRA316JP is somewhat different from the population in the pivotal WA18221 study. In this study CRP was used as a marker for disease activity, there was no requirement for fever or active arthritis. Thus the population may be less severely affected.
- The dosage of tocilizumab in this trial differs from the pivotal study as also children <30 kg received the 8 mg/kg dose.
- The withdrawal design used in this study is inferior for the demonstration of efficacy; however it is used in paediatric studies more often because it is perceived as more ethical. Formally only the need for treatment once it has begun is investigated and not efficacy of treatment itself.

Long term extension study of WA18221 (cut-off 10 May 2010)

The data was cut at the timepoint at which fifty patients had received TCZ treatment for at least one year in study Part II, known as the long-term extension (LTE) cut. As this was an LTE data cut involving escape patients and patients transitioning off of placebo from Part I, the dataset was re-baselined to the first TCZ infusion received in the study. The efficacy endpoints of the LTE data cut are summarized descriptively as there was no placebo comparator for formal statistical analyses to be performed. The efficacy responses observed during the first 12 weeks in Part I of this study were maintained or improved further through to later timepoints beyond one year.

The demographic and disease characteristics at Baseline for Part I of the study and for the LTE cut are comparable.

Efficacy

The primary efficacy endpoint in Part I of the study, JIA ACR30 response with absence of fever, was also assessed at timepoints in the May 10th 2010 LTE cut. As in Part I of the study, the proportion of patients achieving this endpoint was maintained beyond the first 12 weeks with 84.8% of patients responding at Week 72 as follows:

- Week 24, 89.0% (97/109 patients)
- Week 36, 86.1% (93/108 patients)
- Week 48, 82.1% (78/95 patients)
- Week 60, 89.3% (50/56 patients)
- Week 72, 84.8% (28/33 patients)

For the JIA ACR30/50/70/90 endpoints, response was either maintained or improved beyond Week 12. For example JIA ACR90 developed as follows:

- Week 24, 50.5% (55/109 patients)
- Week 36, 60.2% (65/108 patients)
- Week 48, 69.5% (66/95 patients)
- Week 60, 67.9% (38/56 patients)
- Week 72, 69.7% (23/33 patients)

In the WA18221 study, 92.2% (103/112) of patients were receiving oral corticosteroids at Baseline. A reduction from the overall Baseline mean ± SD dose of 0.30 ± 0.20 mg/kg/day oral corticosteroid dose (Baseline range = 0.00 to 1.33 mg/kg/day) was accomplished for 94.2% (97/103) of patients at the time of this LTE cut with 51.5% (53/97) of patients completely eliminating oral corticosteroids as a concomitant medication. Although it is more difficult to assess in a non-randomised trial the rate of discontinuation of corticosteroids or reduction of corticosteroids is considered clinically relevant.

Treatment Completion and Withdrawal

As this study is still on-going, the number of patients completing treatment at specific timepoints decreased as patients either have not reached that week or have withdrawn. Below is the number of patients completing treatment and the number of patients who withdrew up to the specified timepoints.

Week 12: 109 (97%) patients completed treatment, 3 withdrew
Week 24: 109 (97%) patients completed treatment, 3 withdrew
Week 36: 108 (96%) patients completed treatment, 4 withdrew
Week 48: 95 (85%) patients completed treatment, 7 withdrew
Week 60: 56 (50%) patients completed treatment, 11 withdrew
Week 72: 33 (29%) patients completed treatment, 12 withdrew

In the May 10th, 2010 LTE data cut of study WA18221, two patients from the 8 mg/kg TCZ treatment group and two patients from the 12 mg/kg treatment group discontinued due to loss of efficacy. None of these patients had a positive anti-TCZ neutralizing assay.

Patients were offered active treatment after completion of the randomised part of the study. Thus this population includes patients that were randomised to treatment from the beginning, patients that entered via the escape option and patients that entered at the end of the randomised part of the study. The data for the maintenance of effect are reassuring in general and a high proportion of patients reach JIA ACR90. Effects on the endpoints are generally consistent. From the longer term observations it is mentioned that 12 patients discontinued. The reasons for withdrawal were adverse event (4 patients), insufficient therapeutic response (4 patients), refused treatment (2 patients), death (1 patient), and failure to return (1 patient).

Long term extension study of MRA011JP and MRA316JP: MRA317JP

This was an open-label extension study for patients with sJIA who responded to TCZ in studies MRA011JP or MRA316JP. A total of 60 patients were enrolled and received a single dose every two weeks of TCZ in this study

The proportion of patients with a JIA ACR30 response was 88.5% (54/61 patients) after 12 weeks, and then ranged from 85.7% to 100.0% from 24 to 324 weeks after the start of treatment.

Discussion on clinical efficacy

The pivotal trial WA18221 was a randomised, double-blind placebo controlled trial. This design is the preferred choice for the demonstration of efficacy, as there are no approved therapies and an actively controlled study would be difficult to investigate and compare. Therefore a placebo controlled trial is acceptable. The duration of 12 weeks for the blinded portion of the trial is acceptable. A longer placebo controlled phase is not justifiable for patients with active disease.

There is a rather pronounced imbalance in the number of patients that entered the escape option already in phase I of the trial. Possible reasons for receiving escape therapy included fever for three consecutive days, symptomatic serositis requiring increased corticosteroids, JIA ACR30 flare compared to baseline. For the ITT analysis this poses no problem.

Demographic and disease characteristics are generally well balanced. There are some imbalances in CRP that are caused by excessively high values in three individuals. The population included is characterised by a rather high disease activity even though treatment with MTX and corticosteroid is common. About one third of tocilizumab treated patients are ≤6 years, one third 7-12 years and the remaining third >12 years of age.

The patients included had sJIA diagnosed by the currently accepted criteria. The patients had to have signs of active disease and the need for additional treatment. The inclusion of this population is acceptable as it has been shown that patients with the presence of systemic signs of the disease 6 months after onset have a worse prognosis (Spiegel et al. Arthritis Rheum. 2000;43:2402-9). Patients with high corticosteroid doses were excluded. This could exclude the most severe patients that are usually smaller children. However, due to the toxicity of corticosteroid it is common to apply pulse therapy and then reduce doses, it is not practise to maintain patients on high corticosteroid dose. Rather other therapies are introduced. Therefore there is less concern as regards external validity.

From the amendment documentation the changes to the inclusion criteria for disease duration and disease activity could be important. It would be more conservative only to include patients with a definite diagnosis of sJIA and ongoing disease activity 6 months after definite diagnosis. Since diagnosis of sJIA is not straightforward patients included merely on the basis of documented presence of symptoms for more than 6 months may be undertreated and therefore not be totally representative for the population with higher therapeutic need. As regards activity the initial inclusion criteria only asked for presence of specific arthritis severity at screening. However, more important are the baseline characteristics actually observed. In response to questions the MAH supplied information that all patients had a definite diagnosis of sJIA for at least 6 months even though the revised inclusion criteria allowed inclusion of patients with lower disease duration since definite diagnosis therefore these theoretical concerns are alleviated.

Thirty seven patients were randomised to placebo, 37 to tocilizumab 8 mg/kg and 38 to tocilizumab 12 mg/kg. Twenty patients in the placebo group went into escape and received active therapy during the 12 week trial. The majority of included patients were on concomitant MTX and corticosteroid therapy, all had active disease. The majority had been pretreated with biologics. About one third of

tocilizumab treated patients are ≤6 years, one third 7-12 years and the remaining third >12 years of age.

Two different doses of tocilizumab were used in the trial: 8 mg/kg for patients of 30 kg bodyweight or more, and 12 mg/kg for patients of less than 30 mg. These doses were chosen on the basis of a population PK analysis from the Japanese trial with the intention to have a uniform exposure across the range of different body weights.

The chosen primary endpoint JIA ACR30 and absence of fever is acceptable. The addition of absence of fever into the primary endpoint is appropriate as quotidian fever is a hallmark of uncontrolled systemic disease. Currently there are no known specific biomarkers to evaluate activity of systemic disease. Fever and CRP are obvious choices, unfortunately both are directly regulated by IL-6, thus there is the possibility that an effect on these markers will not indicate a true effect on disease activity itself. However, in the absence of better markers fever is acceptable. In addition, it is of high clinical relevance as fever by itself has a detrimental impact on quality of life. The secondary endpoints are acceptable and use subjective as well as objective evaluation of features of systemic disease. This enables the evaluation of efficacy as regards patients with predominant arthritis or predominant systemic disease. For the assessment of joints an independent joint assessor was used that was not involved in patient care and did not have information on clinical course and laboratory values. This procedure is useful to reduce bias in arthritis assessment.

The response criterion used for the primary endpoint (JIA ACR30 and absence of fever) was met by 9/37 patients in the placebo group, 28/37 patients in the tocilizumab 8 mg/kg group and 36/38 patients in the tocilizumab 12 mg/kg group. This result is statistically significant and clinically relevant. The responder rate is even higher in the 12 mg/kg cohort comprising children of less than 30 kg bodyweight. However the study was not powered to detect a difference in the two dosing groups. Sensitivity analyses confirmed robustness of results. All 22 secondary endpoints met the significance level of $p \leq 0.05$. The finding that corticosteroid use could be reduced in patients by more than 20% after reaching a JIA ACR70 response without experiencing a flare of disease is of medical importance as the side effects of corticosteroid therapy contribute to long term morbidity in this population. JIA ACR30 response is reaching a plateau at week 6, responder rates for JIA ACR50 plateau by 8 weeks and JIA ACR70 and 90 continue to rise up to week 12. Sensitivity analyses of efficacy and analyses across differently defined subpopulations (e.g. with or without MTX background therapy) gave consistent results.

Influence of tocilizumab therapy on features of systemic disease gives a slightly heterogeneous picture: while fever, CRP, anaemia, thrombocytosis, leukocytosis and pain all show clear signs of normalisation, rash appears to be less influenced.

Patients from WA18221 have entered a part II long term extension study. Patients were offered active treatment after completion of the randomised part of the study. Thus this population includes patients that were randomised to treatment from the beginning, patients that entered via the escape option and patients that entered at the end of the randomised part of the study. Data cut was at the time when 50 patients had reached one year of treatment. The majority of patients maintain the response for JIA ACR30 and absence of fever, 78/95 patients are responding at weeks 48. The hard to meet response criterium JIA ACR90 was met by 66/95 patients at week 48.

The supportive study MRA316JP used a single arm, open label run in phase followed by a randomised, blinded withdrawal. Generally this design is considered inferior to a blinded placebo controlled trial. The populations of the WA18221 and MRA316JP are not directly comparable since different inclusion criteria were used, in particular CRP elevation was an inclusion criterion but active arthritis was not required. Thus this population may be less severely affected. The trial demonstrated a statistically significant and clinically relevant difference of maintenance of response to the treatment. Although not

regarded as the optimum design for showing efficacy the generated data are seen as supportive for the results of the pivotal WA18221 trial.

Study MRA011JP investigated different doses based on a pharmacodynamic endpoint. Even though a dose of 2 mg/kg was sufficient to lower CRP in the first week further increments were necessary based on the pre-infusion CRP at week 2. Lower tocilizumab trough values are clearly associated with higher CRP and higher ESR. The authors of the study report concluded that the higher dose is therefore more appropriate. Of note CRP under treatment may not be indicative of the underlying disease process anymore it only shows the degree of IL-6R blockade. This study design is insufficient to conclude on the most appropriate dose as it ignores the inevitable time it takes to reach steady state.

Long term extension data from the Japanese trials give a consistent picture with response rate for JIA ACR30 above 85% from 24 to 324 weeks after start of treatment.

Conclusions on clinical efficacy

Short term efficacy has been conclusively demonstrated in the pivotal trial WA18221. Findings within the trial and compared to the supportive studies show a consistent clinically relevant effect. Available long term efficacy data are re-assuring and further follow-up data (WA18221 (phase II and III)) as detailed in the RMP will be generated.

1.3.3. Clinical safety

Study WA18221

Patient exposure

Study WA18221

Exposure during the First 12 Weeks of Controlled Treatment

In Part 1 of the pivotal study WA18221, the median study duration and exposure to trial treatment in patients treated with TCZ (8 and 12 mg/kg based upon BW) were both 12 weeks, while the median study duration and drug exposure in patients receiving placebo were 8.0 and 8.4 weeks, respectively (Table 13).

Table 13: Summary of Duration in Study and Exposure to Trial Treatment at Week 12 by Trial Treatment (Safety Population, all patients that had received one dose and at least one post-dose safety assessment)

	Placebo N = 37	TCZ 8 mg/kg N = 37	TCZ 12 mg/kg N = 38	All TCZ N = 75
Duration in Study (Weeks)				
Mean	7.37	11.98	12.24	12.11
SD	4.893	1.314	0.303	0.950
SEM	0.804	0.216	0.049	0.110
Median	8.00	12.14	12.14	12.14
Min-Max	0.3 - 13.0	4.3 - 13.0	11.7 - 13.0	4.3 - 13.0
Sum	272.7	443.1	465.0	908.1
n	37	37	38	75
Exposure to Trial Treatment (Weeks)				
Mean	7.52	11.91	12.01	11.96
SD	4.699	1.310	0.486	0.978
SEM	0.772	0.215	0.079	0.113
Median	8.43	12.14	12.14	12.14
Min-Max	2.1 - 13.0	4.4 - 12.4	10.1 - 12.6	4.4 - 12.6
Sum	278.3	440.6	456.4	897.0
n	37	37	38	75

Study WA18221 long term extension

In Part II of the pivotal study WA18221, for the May 10 2010 LTE data cut, for the all TCZ group, the median study duration was 1.14 years and median exposure to trial treatment was 1.15 years. The total duration of observation is 132 patient years. This is used as a denominator for comparison.

As shown in Table 14, the majority of patients had received 21 to 40 TCZ infusions by May 10th 2010 data cut.

Table 14 Summary of Number of TCZ Infusions Received by Trial Treatment - May 10th 2010 Data Cut (Study WA18221, Safety Population)

	TCZ 8 MG/KG N = 52	TCZ 12 MG/KG N = 50	TCZ 8 MG/KG to TCZ 12 MG/KG N = 1	TCZ 12 MG/KG to TCZ 8 MG/KG N = 9	All TCZ N = 112
No. of TCZ Infusions Received					
1-5	1 (2%)	2 (4%)	-	-	3 (3%)
11-15	1 (2%)	2 (4%)	-	-	3 (3%)
16-20	5 (10%)	2 (4%)	-	2	9 (8%)
21-25	9 (17%)	12 (24%)	-	3	24 (21%)
26-30	14 (27%)	14 (28%)	-	1	29 (26%)
31-35	6 (12%)	9 (18%)	1	2	18 (16%)
36-40	9 (17%)	7 (14%)	-	1	17 (15%)
41-45	6 (12%)	1 (2%)	-	-	7 (6%)
46-50	1 (2%)	-	-	-	1 (<1%)
51-55	-	1 (2%)	-	-	1 (<1%)
n	52	50	1	9	112

Supportive sJIA Studies

Table 15 provides a summary of the TCZ exposure for the supportive sJIA studies.

Table 15 Total TCZ Exposure in supportive sJIA Studies, Safety population

	MRA011JP/ 316JP/317JP n = 67	MRA324JP n = 82	Total n = 149
Treatment duration (year)			
Mean±SD	3.4±1.6	1.2±0.7	2.2±1.6
Median	3.5	1.2	2.1
(Min - Max)	(0.04 - 6.22)	(0.08 - 2.38)	(0.04 - 6.22)
No. of patients with treatment duration	No. (%)	No. (%)	No. (%)
<1 year	9 (13.4)	34 (41.5)	43 (28.9)
≥ 1 year - <2 years	-	30 (36.6)	30 (20.1)
≥ 2 years - <3 years	4 (6.0)	18 (22.0)	22 (14.8)
≥ 3 years - <4 years	34 (50.7)	-	34 (22.8)
≥ 4 years - <5 years	12 (17.9)	-	12 (8.1)
≥ 5 years	8 (11.9)	-	8 (5.4)
Total patient years	228.0	98.3	326.3

Adverse events

Study WA18221

An overview of AEs with an onset day prior to Week 12 is shown in table 16.

Table 16 Summary of all AE up to week 12, safety population

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
AEs, n	48	72	75	147
No. patients with at least one AE, n (%)	23 (62.2)	33 (89.2)	33 (86.8)	66 (88.0)
SAEs, n	0	1	3	4
No. patients with at least one SAE, n (%)	0	1 (2.7)	2 (5.3)	3 (4.0)
AEs leading to a missed dose	3	7	4	11
No. patients with at least one AE, n (%)	2 (5.4)	7 (18.9)	4 (10.5)	11(14.7)
Infection AEs*, n	14	21	34	55
No. patients with at least one infection AE, n (%)	11 (29.7)	18 (48.6)	23 (60.5)	41 (54.7)
Infection SAEs*, n	0	1	1	2
No. patients with at least one infection SAE, n (%)	0	1 (2.7)	1 (2.6)	2 (2.7)
MAS SAEs, n	0**	0	0	0
Deaths, n	0	0	0	0

The majority of AEs were of mild or moderate intensity in all treatment groups, with 48.6% in the placebo group and 73.3 % in the all TCZ group (TCZ 8 mg/kg group, 78.4% and TCZ 12 mg/kg group, 68.4%) reported as mild in intensity (table 17, 18 and 19).

Table 17 Distribution of severity of AE observed up to week 12, safety population, placebo

Body System/ Adverse Event	Total No. (%)	Intensity: Mild No. (%)	Moderate No. (%)	Severe No. (%)	Life threat No. (%)
ALL BODY SYSTEMS					
Total Pts with at Least one AE	23 (62.2)	18 (48.6)	9 (24.3)	3 (8.1)	-
Total Number of AEs	48	29	12	4	-

Table 18 Distribution of severity of AE observed up to week 12, safety population, tocilizumab 8 mg/kg

Body System/ Adverse Event	Total No. (%)	Intensity: Mild No. (%)	Moderate No. (%)	Severe No. (%)	Life threat No. (%)
ALL BODY SYSTEMS					
Total Pts with at Least one AE	33 (89.2)	29 (78.4)	10 (27.0)	1 (2.7)	-
Total Number of AEs	72	56	13	1	-

Table 19 Distribution of severity of AE observed up to week 12, safety population, tocilizumab 12 mg/kg

Body System/ Adverse Event	Total No. (%)	Intensity: Mild No. (%)	Moderate No. (%)	Severe No. (%)	Life threat No. (%)
ALL BODY SYSTEMS					
Total Pts with at Least one AE	33 (86.8)	26 (68.4)	17 (44.7)	-	1 (2.6)
Total Number of AEs	75	51	21	-	1

As shown in table 20, the most frequently reported AEs in TCZ-treated patients were upper respiratory tract infection, headache, nasopharyngitis, and diarrhea. The most frequently reported AEs in the placebo-treated patients were juvenile arthritis and pyrexia. These events usually led to escape therapy.

Table 20 Summary of AEs with an incidence rate of ≥5% (safety population) to Week 12

Adverse Event	Placebo N = 37 No. (%)	TCZ 8 mg/kg N = 37 No. (%)	TCZ 12 mg/kg N = 38 No. (%)	All TCZ N = 75 No. (%)
UPPER RESPIRATORY TRACT INFECTION	4 (10.8)	4 (10.8)	6 (15.8)	10 (13.3)
HEADACHE	3 (8.1)	5 (13.5)	2 (5.3)	7 (9.3)
NASOPHARYNGITIS	1 (2.7)	2 (5.4)	6 (15.8)	8 (10.7)
DIARRHOEA	1 (2.7)	3 (8.1)	2 (5.3)	5 (6.7)
JUVENILE ARTHRITIS	5 (13.5)	-	2 (5.3)	2 (2.7)
NEUTROPENIA	1 (2.7)	1 (2.7)	2 (5.3)	3 (4.0)
OROPHARYNGEAL PAIN	1 (2.7)	2 (5.4)	1 (2.6)	3 (4.0)
ARTHROPOD BITE	-	1 (2.7)	2 (5.3)	3 (4.0)
BACK PAIN	-	1 (2.7)	2 (5.3)	3 (4.0)
GASTROENTERITIS VIRAL	-	1 (2.7)	2 (5.3)	3 (4.0)
PHARYNGITIS	2 (5.4)	1 (2.7)	1 (2.6)	2 (2.7)
PYREXIA	6 (16.2)	-	-	-
URTICARIA	-	-	3 (7.9)	3 (4.0)
VOMITING	-	2 (5.4)	1 (2.6)	3 (4.0)
COUGH	1 (2.7)	2 (5.4)	-	2 (2.7)
DIZZINESS	1 (2.7)	2 (5.4)	-	2 (2.7)
HAEMATURIA	1 (2.7)	-	2 (5.3)	2 (2.7)
ABDOMINAL PAIN	-	-	2 (5.3)	2 (2.7)
DYSMENORRHOEA	-	2 (5.4)	-	2 (2.7)
GASTROINTESTINAL DISORDER	-	2 (5.4)	-	2 (2.7)
INFLUENZA LIKE ILLNESS	2 (5.4)	1 (2.7)	-	1 (1.3)
JOINT SPRAIN	-	2 (5.4)	-	2 (2.7)

There was one life-threatening event in the tocilizumab 12 mg/kg group. This was a 3 year old male who developed urticaria on study day 29 following the week 4 tocilizumab infusion. He received the week 6 infusion without incident. On day 57 he developed life-threatening angioedema during tocilizumab infusion and was discontinued from treatment.

Study WA18221 long term extension

Table 21 Distribution of severity of AE, safety population, tocilizumab 8 mg/kg

Body System/ Adverse Event	Total No. (%)	Intensity: Mild No. (%)	Moderate No. (%)	Severe No. (%)	Life threat No. (%)
ALL BODY SYSTEMS					
Total Pts with at Least one AE	51 (98.1)	50 (96.2)	31 (59.6)	5 (9.6)	1 (1.9)
Total Number of AEs	345	242	86	7	3

Table 22 Distribution of severity of AE, safety population, tocilizumab 12 mg/kg

Body System/ Adverse Event	Total No. (%)	Intensity: Mild No. (%)	Moderate No. (%)	Severe No. (%)	Life threat No. (%)
ALL BODY SYSTEMS					
Total Pts with at Least one AE	49 (98.0)	47 (94.0)	35 (70.0)	6 (12.0)	1 (2.0)
Total Number of AEs	409	303	90	8	1

The spectrum of AE in the extension study seems comparable, as expected incidence is increasing. Most AEs are more common in the 12 mg/kg cohort.

The most frequently reported AEs were nasopharyngitis, upper respiratory tract infection, juvenile arthritis, cough, diarrhea, headache, neutropenia, vomiting, and rash (Table 23).

Table 23 Summary of AEs with an incidence rate of ≥5% (safety population) - May 10th, 2010 Data Cut

Adverse Event	TCZ 8 MG/KG N = 52 No. (%)	TCZ 12 MG/KG N = 50 No. (%)	TCZ 8 MG/KG to TCZ 12 MG/KG N = 1 No. (%)	TCZ 12 MG/KG to TCZ 8 MG/KG N = 9 No. (%)	All TCZ N = 112 No. (%)
NASOPHARYNGITIS	14 (26.9)	14 (28.0)	-	5	33 (29.5)
UPPER RESPIRATORY TRACT INFECTION	14 (26.9)	17 (34.0)	-	1	32 (28.6)
JUVENILE ARTHRITIS	9 (17.3)	15 (30.0)	1	2	27 (24.1)
COUGH	6 (11.5)	13 (26.0)	-	1	20 (17.9)
DIARRHOEA	11 (21.2)	6 (12.0)	-	-	17 (15.2)
HEADACHE	8 (15.4)	9 (18.0)	-	-	17 (15.2)
NEUTROPENIA	6 (11.5)	9 (18.0)	-	1	16 (14.3)
VOMITING	5 (9.6)	8 (16.0)	-	-	13 (11.6)
RASH	5 (9.6)	6 (12.0)	-	1	12 (10.7)
ARTHROPOD BITE	2 (3.8)	7 (14.0)	-	2	11 (9.8)
NAUSEA	5 (9.6)	4 (8.0)	-	2	11 (9.8)
OROPHARYNGEAL PAIN	8 (15.4)	3 (6.0)	-	-	11 (9.8)
RHINITIS	2 (3.8)	8 (16.0)	-	1	11 (9.8)
EAR INFECTION	2 (3.8)	8 (16.0)	-	-	10 (8.9)
GASTROENTERITIS VIRAL	3 (5.8)	6 (12.0)	-	1	10 (8.9)
GASTROENTERITIS	4 (7.7)	4 (8.0)	-	1	9 (8.0)
INFLUENZA LIKE ILLNESS	4 (7.7)	5 (10.0)	-	-	9 (8.0)
OTITIS MEDIA	4 (7.7)	5 (10.0)	-	-	9 (8.0)
ABDOMINAL PAIN	4 (7.7)	4 (8.0)	-	-	8 (7.1)
ABDOMINAL PAIN UPPER	2 (3.8)	6 (12.0)	-	-	8 (7.1)
ARTHRALGIA	5 (9.6)	3 (6.0)	-	-	8 (7.1)
BACK PAIN	4 (7.7)	2 (4.0)	-	2	8 (7.1)
IMPETIGO	1 (1.9)	6 (12.0)	1	-	8 (7.1)
VIRAL INFECTION	3 (5.8)	4 (8.0)	-	1	8 (7.1)
VIRAL UPPER RESPIRATORY TRACT INFECTION	5 (9.6)	2 (4.0)	-	1	8 (7.1)
URTICARIA	3 (5.8)	3 (6.0)	-	1	7 (6.3)
BRONCHITIS	2 (3.8)	4 (8.0)	-	-	6 (5.4)
CONJUNCTIVITIS	1 (1.9)	4 (8.0)	-	1	6 (5.4)
JOINT SPRAIN	4 (7.7)	1 (2.0)	-	1	6 (5.4)
NASAL CONGESTION	3 (5.8)	2 (4.0)	-	1	6 (5.4)
PAIN IN EXTREMITY	4 (7.7)	2 (4.0)	-	-	6 (5.4)
PHARYNGITIS	4 (7.7)	1 (2.0)	-	1	6 (5.4)
TRANSAMINASES INCREASED	5 (9.6)	1 (2.0)	-	-	6 (5.4)

Serious adverse events and deaths

Deaths

A total of 9 deaths were reported, 1 in study WA18221, 2 in the supportive sJIA studies, 3 in the post marketing program, 1 in the MAH's TCZ compassionate use program, and 2 in the TCZ compassionate use program in Japan.

WA18221: No deaths were reported during the first 12 weeks of study treatment. A 16 year-old male patient died of suspected tension pneumothorax on study Day 349. The investigator considered the death unrelated to study treatment.

Chugai studies: A 3 year-old girl, died of MAS 15 days following the 4th TCZ dose administration.
A 22 year old male patient died of arrhythmia secondary to his cardiac amyloidosis 8 days following the 7th TCZ dose administration.

Postmarketing: A 22 month-old female in the JPMS sJIA program died from acute respiratory distress syndrome, multiple confounding factors were present. A 4 month-old male in the JPMS sJIA program died from pseudomonas infection, sepsis and interstitial lung disease following pancytopenia.
A 45 year-old male receiving TCZ for adult onset Still's disease died from megacolon and multi-organ failure. The narrative of this case is inconclusive.

Compassionate program: A 5 year old female patient who died of acute myeloid leukemia (AML) whilst receiving tocilizumab for systemic juvenile rheumatoid arthritis. The patient also had interstitial pneumonia that apparently developed during treatment with tocilizumab. She was treated with cyclophosphamide for interstitial pneumonia. After development of AML she continually deteriorated with possible infection, possible sJIA flare and progression of AML. No chemotherapy was administered and tocilizumab was not implicated in the death.

A 4-year-old female patient died whilst receiving tocilizumab for the treatment of systemic juvenile idiopathic arthritis. Tocilizumab was used as a rescue treatment because her sJIA had worsened dramatically and no other treatments were available.

Serious adverse events

WA18221: There were 3 patients with 4 SAE in the controlled phase of the trial: bacterial arthritis (tocilizumab 8 mg/kg), angioedema and urticarial (tocilizumab 12 mg/kg), varicella (tocilizumab 12 mg/kg. The varicella infection during treatment with tocilizumab resolved without sequelae, the patient was treated with acyclovir and resumed treatment after temporary discontinuation. All other SAE resolved without sequelae. There were no SAE in the placebo group.

Including the extension phase there were 32 SAE in 25 treated patients: gastroenteritis 3 cases, varicella 3 cases, pneumonia 3 cases, bacterial arthritis 1 case, bronchopneumonia 1 case, gastroenteritis one case, herpes zoster 1 case, otitis media 1 case, pharyngotonsillitis 1 case, URTI 1 case, femur fracture 1 case, forearm fracture 1 case, unspecified fracture 1 case, joint dislocation 1 case, HLH/MAS 3 cases, pneumothorax 1 case, pulmonary veno-occlusive disease 1 case, angioedema 1 case, urticaria 1 case, cardiac failure 1 case, gastritis 1 case, influenza-like illness 1 case, transaminase increased 2 cases, dehydration 1 case.

Laboratory findings

Neutropenia

Study WA18221

A total of four patients experienced AEs of neutropenia to Week 12. All events resolved and were not associated with any serious infections.

Overall, the lowest neutrophil count during the 12-week treatment period remained in the normal range in 78.7% of the TCZ-treated patients compared with 100% of patients in the placebo group Table 24).

Table 24 Summary of the Worst CTC Grades for Neutrophils to Week 12 by Trial Treatment (Safety Population, Study WA18221)

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
Neutrophils				
Overall				
n	35	37	38	75
NORMAL	35 (100.0%)	30 (81.1%)	29 (76.3%)	59 (78.7%)
GRADE -1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GRADE -2	0 (0.0%)	4 (10.8%)	6 (15.8%)	10 (13.3%)
GRADE -3	0 (0.0%)	2 (5.4%)	3 (7.9%)	5 (6.7%)
GRADE -4	0 (0.0%)	1 (2.7%)	0 (0.0%)	1 (1.3%)

The incidence of neutropenia <1.0/nl in this 12 week trial was 6/75 = 8% which seems higher than the incidence observed in adults in the longer lasting pivotal trials (3.4%), also considering the shorter duration of the trial. The reference range for neutrophils in the investigated age group is comparable to the adult age group, therefore under- or overestimation of incidence is unlikely.

Study WA18221 long term extension

Overall in 112 patients, the lowest neutrophil count remained in the normal range in 59 TCZ-treated patients (52.7%) (table 25). The lowest neutrophil count was CTC grade 1 in 5 patients (4.5%), CTC grade 2 in 31 patients (27.7%), CTC grade 3 in 15 patients (13.4%), and CTC grade 4 in 2 patients (1.8%).

Table 25 Summary of Worst CTC Grades for Neutrophil Count (Hypo) by Trial Treatment - May 10th Data Cut

	TCZ 8 MG/KG (N=52)	TCZ 12 MG/KG (N=50)	TCZ 8 MG/KG to TCZ 12 MG/KG (N=1)	TCZ 12 MG/KG to TCZ 8 MG/KG (N=9)	All TCZ (N=112)
Neutrophils					
Overall					
n	52	50	1	9	112
NORMAL	31 (59.6%)	23 (46.0%)	1 (100.0%)	4 (44.4%)	59 (52.7%)
GRADE -1	5 (9.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
GRADE -2	11 (21.2%)	18 (36.0%)	0 (0.0%)	2 (22.2%)	31 (27.7%)
GRADE -3	5 (9.6%)	7 (14.0%)	0 (0.0%)	3 (33.3%)	15 (13.4%)
GRADE -4	0 (0.0%)	2 (4.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

In the extension phase incidence of neutropenia increases considerably. Of the 17 patients (15%) with a neutrophil count depression to CTC grade 3 or 4, 7 had the depression of the neutrophil count at a single time point, 9 had non-consecutive neutrophil count depressions, and 1 had consecutive neutrophil count depressions. Both of the 2 patients with a CTC grade 4 neutrophil count depression had the depression of the neutrophil count at a single time point. Of note there is no clear correlation between neutropenia AE and infection AE.

Thrombocytopenia

Study WA18221

Two patients (one in the placebo group and one in the TCZ 12 mg/kg) had depression in platelets of ≤100/nL at a single time point. No patient had a depression in platelets of ≤50/nL in the study (Table 26).

Table 26 Summary of the Worst CTC Grades for thrombocytopenia to Week 12 (Safety Population, Study WA18221)

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
Platelets				
Overall				
n	34	37	38	75
NORMAL	33 (97.1%)	35 (94.6%)	34 (89.5%)	69 (92.0%)
GRADE -1	1 (2.9%)	2 (5.4%)	4 (10.5%)	6 (8.0%)

Study WA18221 long term extension

During study treatment, the lowest platelet count remained normal in 76.8% of patients, with 22.3% of patients experiencing CTC grade 1 thrombocytopenia and 1 patient (0.9%) having CTC grade 3 thrombocytopenia (Table 27).

Table 27 Summary of Worst CTC Grades for Platelet Count (Hypo) by Trial Treatment - May 10th Data Cut

	TCZ 8 MG/KG (N=52)	TCZ 12 MG/KG (N=50)	TCZ 8 MG/KG to TCZ 12 MG/KG (N=1)	TCZ 12 MG/KG to TCZ 8 MG/KG (N=9)	All TCZ (N=112)
Platelets					
Overall					
n	52	50	1	9	112
NORMAL	44 (84.6%)	33 (66.0%)	1 (100.0%)	8 (88.9%)	86 (76.8%)
GRADE -1	7 (13.5%)	17 (34.0%)	0 (0.0%)	1 (11.1%)	25 (22.3%)
GRADE -3	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

Mean platelet value decreased in tocilizumab treated patients. This is expected and could be regarded as a pharmacodynamic marker for anti-inflammatory activity of the drug. In the extension phase there is a considerable increase of CTC grade 1 thrombocytopenia (CTC grade 1: <LLN - 75/nL) compared to the 12 week study phase.

AST, ALT and bilirubin elevation

Study WA18221

Similarly to adults treatment with tocilizumab causes AST/ALT elevation in a fraction of the patients. In the TCZ-treated patients mean absolute ALT values were elevated at Week 2 that gradually decreased through Week 12 in the 4 to 6 years age group and 7 to 9 years age group. However, in the older age group (10 to 17 years), the mean absolute ALT values decreased at Week 2 but stayed higher than the placebo group throughout the study especially in the TCZ 8 mg/kg group. Similar to the ALT, in patients who were treated with TCZ, elevations in mean AST (U/L) were observed from Week 2 that gradually decreased through Week 12 in the 4 – 6 years age group and 7 to 9 years age group. However, in the older age group (10 to 17 years), AST decreased at Week 2 but stayed higher than the placebo group throughout the study especially in the TCZ 8 mg/kg group.

Mean values of absolute total, direct, and indirect bilirubin values remained within the normal range from baseline to Week 12 in all age groups and in all treatment groups. Between Week 2 and Week 12, the absolute direct, indirect, and total bilirubin values were slightly higher in the TCZ 8 mg/kg group compared with the TCZ 12 mg/kg and the placebo groups.

There were a total of 21 occasions in which an ALAT value > ULN and a total bilirubin value > ULN occurred in a same time window for a given patient. 10 of these 21 had an ALAT elevation up to threefold and bilirubin elevation up to two fold.

One patient met the criteria of "Hy's law", this patient had pre-existing hepatic steatosis and transaminase levels normalised after discontinuation of therapy.

Table 28 Summary of ALT, AST, and Bilirubin Values by CTC Grade to Week 12 (Study WA18221, Safety Population)

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
ALAT (SGPT)				
Overall				
n	35	37	38	75
NORMAL	32 (91.4%)	24 (64.9%)	29 (76.3%)	53 (70.7%)
GRADE 1	3 (8.6%)	8 (21.6%)	8 (21.1%)	16 (21.3%)
GRADE 2	0 (0.0%)	4 (10.8%)	1 (2.6%)	5 (6.7%)
GRADE 3	0 (0.0%)	1 (2.7%)	0 (0.0%)	1 (1.3%)
ASAT (SGOT)				
Overall				
n	35	37	38	75
NORMAL	35 (100.0%)	24 (64.9%)	37 (97.4%)	61 (81.3%)
GRADE 1	0 (0.0%)	11 (29.7%)	1 (2.6%)	12 (16.0%)
GRADE 2	0 (0.0%)	2 (5.4%)	0 (0.0%)	2 (2.7%)
Total Bilirubin				
Overall				
n	35	37	38	75
NORMAL	35 (100.0%)	35 (94.6%)	37 (97.4%)	72 (96.0%)
GRADE 1	0 (0.0%)	1 (2.7%)	1 (2.6%)	2 (2.7%)
GRADE 2	0 (0.0%)	1 (2.7%)	0 (0.0%)	1 (1.3%)

Study WA18221 long term extension

ALT values remained in the normal range throughout study treatment in 51.8% of patients in the all TCZ group, and CTC grade 1, 2, and 3 ALT elevations were observed in 32.1%, 8.9%, and 7.1% of patients, respectively (Table 29).

Table 29 Summary of Worst CTC Grades for ALT (Hyper) by Trial Treatment - May 10th 2010 Data Cut (Study WA18221, Safety Population)

	TCZ 8 MG/KG (N=52)	TCZ 12 MG/KG (N=50)	TCZ 8 MG/KG to TCZ 12 MG/KG (N=1)	TCZ 12 MG/KG to TCZ 8 MG/KG (N=9)	All TCZ (N=112)
ALAT (SGPT)					
Overall					
n	52	50	1	9	112
NORMAL	24 (46.2%)	29 (58.0%)	1 (100.0%)	4 (44.4%)	58 (51.8%)
GRADE 1	13 (25.0%)	18 (36.0%)	0 (0.0%)	5 (55.6%)	36 (32.1%)
GRADE 2	8 (15.4%)	2 (4.0%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
GRADE 3	7 (13.5%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)

Cholesterol

The mean change in baseline and absolute values in total cholesterol in all age groups and treatment groups were within the reference ranges (2.95 to 5.25 mmol/L), except for one patient. The mean plot of change from baseline in lipid cholesterol demonstrated that at Week 2, mean levels increased and then decreased to Week 12 in all age groups except for the 15 to 17 years group which showed continued elevation of lipid cholesterol in the TCZ 12 mg/kg group related to one patient. The mean change from baseline and absolute values in LDL-cholesterol and HDL-cholesterol in all age groups and treatment groups were within reference ranges.

Lipid parameters that were assessed included total cholesterol, LDL-cholesterol, and HDL-cholesterol. The total cholesterol parameters at Baseline, Week 2, and Week 12 are summarized in the table 30 using categories of "normal", "> ULN to 1.5 × ULN", and "> 1.5 to 2 × ULN".

Table 30 Summary of the Extent of Abnormalities in total cholesterol to Week 12 by Trial Treatment (Study WA18221, Safety Population)

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
Total Cholesterol				
Baseline				
n	34	33	34	67
NORMAL	32 (94.1%)	31 (93.9%)	33 (97.1%)	64 (95.5%)
>ULN - 1.5*ULN	2 (5.9%)	2 (6.1%)	1 (2.9%)	3 (4.5%)
>1.5*ULN - 2*ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 2				
n	34	33	35	68
NORMAL	32 (94.1%)	23 (69.7%)	23 (65.7%)	46 (67.6%)
>ULN - 1.5*ULN	2 (5.9%)	9 (27.3%)	12 (34.3%)	21 (30.9%)
>1.5*ULN - 2*ULN	0 (0.0%)	1 (3.0%)	0 (0.0%)	1 (1.5%)
Week 12				
n	16	33	34	67
NORMAL	14 (87.5%)	28 (84.8%)	29 (85.3%)	57 (85.1%)
>ULN - 1.5*ULN	2 (12.5%)	5 (15.2%)	5 (14.7%)	10 (14.9%)
>1.5*ULN - 2*ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

AE of special interest

Infection AE (Safety population)

A higher incidence of infection AEs was reported in patients receiving TCZ (54.7%) than in patients receiving placebo (29.7%) (Table 31). The overall infection AE rate was 287.0 per 100 patient-years for placebo and 344.7 per 100 patient-years for TCZ.

Table 31 Summary of Infection Adverse Events to Week 12, (Study WA18221, Safety Population)

Body System/ Adverse Event	Placebo N = 37 No. (%)	TCZ 8 mg/kg N = 37 No. (%)	TCZ 12 mg/kg N = 38 No. (%)	All TCZ N = 75 No. (%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE	11 (29.7)	18 (48.6)	23 (60.5)	41 (54.7)
Total Number of AEs	14	21	34	55
INFECTIONS AND INFESTATIONS				
Total Pts With at Least one AE	11 (29.7)	14 (37.8)	20 (52.6)	34 (45.3)
UPPER RESPIRATORY TRACT INFECTION	4 (10.8)	4 (10.8)	6 (15.8)	10 (13.3)
NASOPHARYNGITIS	1 (2.7)	2 (5.4)	6 (15.8)	8 (10.7)
GASTROENTERITIS VIRAL	-	1 (2.7)	2 (5.3)	3 (4.0)
PHARYNGITIS	2 (5.4)	1 (2.7)	1 (2.6)	2 (2.7)
VIRAL INFECTION	-	1 (2.7)	1 (2.6)	2 (2.7)
VIRAL UPPER RESPIRATORY TRACT INFECTION	-	1 (2.7)	1 (2.6)	2 (2.7)
INFECTED BITES	1 (2.7)	-	1 (2.6)	1 (1.3)
ARTHRITIS BACTERIAL	-	1 (2.7)	-	1 (1.3)
BRONCHITIS	-	-	1 (2.6)	1 (1.3)
CANDIDIASIS	-	1 (2.7)	-	1 (1.3)
CONJUNCTIVITIS INFECTIVE	-	-	1 (2.6)	1 (1.3)
FOLLICULITIS	-	-	1 (2.6)	1 (1.3)
GASTROENTERITIS	-	-	1 (2.6)	1 (1.3)
HORDEOLUM	-	-	1 (2.6)	1 (1.3)
IMPETIGO	-	-	1 (2.6)	1 (1.3)
ORAL HERPES	-	1 (2.7)	-	1 (1.3)
OTITIS MEDIA VIRAL	-	-	1 (2.6)	1 (1.3)
PNEUMONIA MYCOPLASMAL	-	-	1 (2.6)	1 (1.3)
RHINITIS	-	-	1 (2.6)	1 (1.3)
SINUSITIS	-	1 (2.7)	-	1 (1.3)
TINEA VERSICOLOUR	-	1 (2.7)	-	1 (1.3)
TONSILLITIS	-	1 (2.7)	-	1 (1.3)
TOOTH ABSCESS	-	-	1 (2.6)	1 (1.3)
URINARY TRACT INFECTION	-	1 (2.7)	-	1 (1.3)
VARICELLA	-	-	1 (2.6)	1 (1.3)
ENTEROVIRUS INFECTION	1 (2.7)	-	-	-

(body system continuing ...)

The percentage of patients with infection AEs in the TCZ 12 mg/kg group (60.5%) was higher than in the TCZ 8 mg/kg group (48.6%). In the 12 week controlled phase, the rate of serious infections in the

tocilizumab group was 11.5 per 100 patient years. At one year in the ongoing open label extension phase the overall rate of serious infections remained stable at 11.3 per 100 patient years.

In the ongoing open label extension phase (Part II), the overall rate of infections remained similar at 306.6 per 100 patient years.

The majority of infection AEs in all treatment groups (95.0%) occurred in association with the neutrophil counts $\geq$ the lower limit of normal range (LLN) within 21 days prior to the start of the infection (Table 32).

Table 32 Summary of Total Number of Infection Adverse Events by Neutrophil Counts (12 Week Results)

Total Number of AEs					
	< 500 10^6/L n (%)	500 – 1000 10^6/L n (%)	1000 - < LLN 10^6/L n (%)	≥ LLN n (%)	Missing n (%)
Placebo (N=37)	0	0	0	14 (93.3)	1 (6.7)
TCZ 8 mg/kg (N=37)	0	0	0	21 (100.0)	0
TCZ 12 mg/kg (N=38)	0	2 (5.1)	0	36 (92.3)	1 (2.6)
ALL TCZ (N=75)	0	2 (3.3)	0	57 (95.0)	1 (1.7)

Immunological events

Immunogenicity

In study WA18221, patients were tested for anti-TCZ antibodies. All patients were tested at baseline and Week 12 for anti-TCZ antibodies. Only 1 patient with assay results was positive for confirmation and was also positive for neutralizing assay at Week 12 at the time of the data cut (Table 33).

Table 33 Summary of Patients with any Positive Anti-TCZ Assay Result

	BASELINE N (%)	WEEK 12 N (%)
No. of Patients Tested	67 (89.3%)	65 (86.7%)
No. of Patients with Positive Screening Assay	4 (6.0%)	2 (3.1%)
No. of Patients with Positive Confirmation Assay	0	1 (1.5%)
No. of Patients with Positive Neutralizing Assay	0	1 (1.5%)

Discontinuation due to AE

Study WA18221

Four patients withdrew due to SAEs in the study. One patient withdrew from study treatment on Day 57 due to a life threatening SAE (angioedema).

A second patient randomized to the placebo group escaped at Week 2 to TCZ 12 mg/kg and then withdrew early from the study on Day 70 due to a SAE of MAS/HLH that was possibly related to study treatment. The event resolved after the Week 12 cut.

In the extension one patient withdrew because of an AE of ALT increase.

Another patient withdrew because of pulmonary veno-occlusive disease. This was considered a life-threatening event. The patient also had lung infection on study Day 376, cardiac failure on study Day

384, PVOD on study Day 388, and MAS/HLH on study Day 397. The last dose of study medication was administered on study Day 379 followed by sJIA relapse, which may have triggered the event of HLH/MAS.

Diagnosis of HLH/MAS is difficult. MAS is expected in this population and the differentiation whether it is caused by study drug or disease is cumbersome. The first of the described patients obviously had a high disease activity as she was already moved to the escape arm after 2 weeks. Of note, from the narrative it appears that she had infusion reactions on day 31, day 43 and therefore was hospitalised for the week 8 infusion. Following this infusion she had fever and laboratory changes consistent with developing MAS. She was treated accordingly and tocilizumab treatment was stopped.

Pulmonary veno-occlusive disease is a rare disease, the aetiology is unknown. It has been described associated with auto-immune disease such as scleroderma or CREST, associated with virus infection, as complication of haematopoetic stem cell transplantation and as complication of chemotherapies and radiation. There are a number of confounding factors for the described patient and relation to study drug remains uncertain.

Discussion on clinical safety

The safety profile of tocilizumab has been previously characterised in the adult population. The available database in adults was acceptable and provided sufficient information for the authorisation of the medicinal product. The assessment of safety data in this paediatric population is in general challenging, especially as regards relatedness, as there are multiple confounding factors: the patient population is rather ill, there is a high rate of concomitant therapy with partially overlapping AE profile (e.g. MTX) and the duration of the placebo-controlled phase is only 12 weeks. Therefore this discussion will focus on AE and not on ADR.

Safety data from uncontrolled trials are limited with respect to exposed patients and duration of exposure: 73 patients from the pivotal trial have been exposed to more than 25 infusions corresponding to more than one year of treatment. Furthermore the analysis is hampered by the fact that children less than 30 kg received a higher dose of 12mg/kg compared to a dose of 8 mg/kg in children of more than 30 kg. Of note, the recommended dose for adults is 8 mg/kg every 4 weeks compared with 8 mg/kg every 2 weeks for children.

The observed type of AE in children are rather similar to the adult population, namely infections, leukocytopenia, thrombocytopenia, elevation of ALAT, ASAT, bilirubin and cholesterol and infusion reactions. The rate of AE in children appears to be higher than in the adult population, especially for infections and leukocytopenia. In addition the rate of AE is higher in the 12 mg/kg cohort although this is confounded by the age of the patients and the higher use of MTX and corticosteroids in this age group. The majority of AE were mild to moderate. Considering this higher incidence of treatment related AEs, the possibility of dose reduction or prolonging dosing interval for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients should be studied. The MAH will perform a study to investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients as detailed in the RMP.

In the controlled phase of the pivotal trial there was one case of bacterial arthritis. Non-surgical bacterial arthritis is more common in adults with rheumatoid arthritis. It is no entirely clear whether this is related to the disease or its treatments. In this case intra-articular injections were performed previously and are more likely to be the cause of bacterial arthritis. However, given that the rate of infections is higher in tocilizumab it is conceivable that the risk for haematogenous bacterial arthritis is also increased. The MAH will collect further information on bacterial arthritis to gain a better understanding on this issue as detailed in the RMP. The majority of reported serious AE were a mix of

bacterial and presumably viral infections without a clear pattern. There was no opportunistic infection with the exception of a herpes zoster. Again AE rate was higher in the higher dose group.

Neutropenia was more common in the paediatric population, similarly to the adult population there is no clear correlation to infectious AE although this could well be caused by the limited database. At present it is not clear whether neutropenia is caused by deficient production in the bone marrow or different distribution between circulating and e.g. marginating pool. Increased consumption is regarded as a less likely explanation for neutropenia. Currently management of neutropenia should take general medical knowledge into account, i.e. neutropenia should be avoided and treatment should be delayed or discontinued if severe neutropenia is detected pre-dosing. This event is described in the product information and followed through routine pharmacovigilance activities and additional surveillance through registries and studies as detailed in the RMP.

Similarly to the adult population thrombocytopenia was observed, the degree of thrombocytopenia was not critical and no bleeding events were observed associated with thrombocytopenia.

The elevation of cholesterol has already been observed in adults. The absolute values of cholesterol and the increments are small and not regarded as critical on a population basis. However, for an individual with elevated baseline values this increase could become relevant. Currently it is unknown if sJIA is an independent risk factor for cardiovascular disease as has been shown for rheumatoid arthritis in adults. Therefore it cannot be determined whether the decrease in inflammation, which should reduce cardiovascular risk, is offset by an increase in cholesterol. Currently there is preciously little information at all about the long term fate of paediatric patients with sJIA once they reach adulthood. Further data will be collected in the proposed registries as detailed in the RMP to further characterise the safety profile.

Infection AE were more common in tocilizumab treated patients than in placebo treated patients. Considering the mechanism of action this is not unexpected. The differences in AE are driven by a variety of bacterial as well as viral infections, there is no clear picture emerging. Two cases of zoster were observed. There were two non-serious infections in one patients associated with moderate neutropenia. The patient experienced an episode of infectious conjunctivitis and a tooth abscess. Neutrophil counts were not collected at the day of the AE. In the extension phase number of infection AE were clearly higher in the 12 mg/kg cohort, again a mixture of bacterial and viral disease was observed.

There were no confirmed anti-drug antibody (ADA) positive patients at baseline. One patient was confirmed to be ADA positive at week 12; this patient had experienced serious angioedema and was withdrawn from the study. One additional patient in the 12 mg/kg cohort had confirmed ADA, which were preceded by infusion reactions. There were no further cases of confirmed ADA in the pivotal trial and the extension. In patients that were withdrawn from treatment for lack of efficacy no ADA were found. However, all ADA data in antibody therapies can be misleading because of the long half-life of antibodies and the known problems with the determination of ADA in the presence of active drug. Further data in the longer term are required since it is likely that background therapy will be reduced under continued tocilizumab treatment and immunogenicity might change. Of note, the assay for the determination of ADA performs less well in children because of higher drug levels. A higher rate of false negative results is a possibility.

There was one death from suspected pneumothorax which was also recorded as SAE. Incidence of spontaneous pneumothorax has been reported to be around 18/100,000 per year. It occurs more commonly in young males as in this case. Analysis of all cases in the tocilizumab database revealed confounding factors in the majority of cases.

The population of sJIA is especially challenging as one of the major complications of disease MAS can be triggered by infectious complications as well as insufficient treatment. Therefore a recurring issue apparent from the narratives is the difficult differential diagnosis of infection vs. flare of sJIA vs. triggering of MAS. Often multimodal treatment is instituted directed against infection as well as sJIA flare. From the provided data including a dedicated report on the adjudication procedure for the evaluation of MAS there is no indication that tocilizumab causes MAS. The incidence of MAS reported in the studies and the postmarketing setting from Japan is in either at or below what has been published previously. Given the uncertainties of previous estimates and the uncertainties of the estimates under treatment with tocilizumab further data must be collected. At present it is not possible to give clear treatment recommendations for continuation or discontinuation of therapy. These investigations are important and the MAH will report them with upcoming PSURs especially since drug exposure is considerably higher in children.

Upon request from the CHMP the MAH has further analysed the data from children <5 years of age at baseline to the older children. The higher rate in the observed AE in the smaller age group are mostly in the rate of infections e.g. upper respiratory tract infection, nasopharingitis and rhinitis. It is agreed that there are a number of confounding factors when comparing <5 year old children to the older children, namely higher MTX use, more frequent use of corticosteroids, higher corticosteroid dose and the general fact that infections are more prevalent in smaller children. Abnormalities in the laboratory parameters between the two age groups were comparable and only small differences were observed in number of patients experiencing grade 1 platelet decrease or grade 1 ALT increases. It is also encouraging that only 3 children <5 years of age at baseline had to be withdrawn from the treatment (one due to insufficient response, other failed to return to the treatment and the third due to anaphylactic reaction).

The conclusion of similar safety is based on a relatively small number of cases. The additional data from the pooled Japanese studies appear to confirm the safety profile in the smaller children and support the proposed age range. Further postmarketing observation and particularly the data generation through registries, as agreed in the risk management plan, will be performed.

Conclusions on clinical safety

The qualitative safety profile of tocilizumab in children appears to be generally comparable to adults. However, infections and infestations and neutropenia appear to be more common than in adults. Of note, there is no clear association of neutropenia and infection. So far no serious opportunistic infections have been observed. Elevation of transaminases is also observed frequently, the clinical significance of this observation remains to be under monitoring.

Overall, based on the available data the safety profile in this patient population is considered acceptable. The SmPC provides adequate information and guidance related to the safety concerns. In addition, the measures included in the risk management plan are appropriate to generate further data which will confirm the safety profile. The MAH will perform a study to investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients as detailed in the RMP.

1.3.4. Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan:

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	Proposed Risk Minimization Activities (Routine and Additional)
Identified risks		
Serious infections	• Routine pharmacovigilance • Special CRF for events of special interest: implemented in clinical trials as of Q4 2007/Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT	Routine risk minimization by means of labelling SPC Section 4.3 Contraindications Active, severe infections (see section 4.4) SPC Section 4.4 Special warnings and precautions for use *Infections* Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra (see section 4.8). RoActemra treatment should not be initiated in patients with active infections (see section 4.3). Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes) which may predispose patients to infections. Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for moderate to severe RA or sJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (which includes younger children with sJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA patients, should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Identified risks		
Serious infections (cont'd)		SPC Section 4.8 Undesirable effects Infections In the 6-month, controlled studies the rate of all infections reported with tocilizumab 8 mg/kg plus DMARD treatment was 127 events per 100 pt-yrs compared to 112 events per 100 pt-yrs in the placebo plus DMARD group. In the all exposure population, the overall rate of infections with RoActemra was 108 events per 100 pt-yrs exposure. In 6-month, controlled clinical studies, the rate of serious infections with tocilizumab 8 mg/kg plus DMARDs was 5.3 events per 100 pt-yrs exposure compared to 3.9 events per 100 pt-yrs exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 pt-yrs of exposure in the tocilizumab group and 1.5 events per 100 pt-yrs of exposure in the MTX group. In the long-term exposure population, the overall rate of serious infections (bacterial, viral, fungal) was 4.7 events per 100 pt-yrs. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii pneumonia, cellulitis, Herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported. sJIA: In the 12 week controlled phase, the rate of all infections in the tocilizumab group was 344.7 per 100 patient-years and 287.0 per 100 patient-years in the placebo group. In the on-going open label extension phase (Part II) the overall rate of infections remained similar at 306.6 per 100 patient- years. In the 12 week controlled phase

		the rate of serious infections in the tocilizumab group was 11.5 per 100 patient years. At one year in the on-going open label extension phase the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Identified risks		
Serious infections (cont'd)		Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Do not use RoActemra If you have an active, severe infection. Take special care with RoActemra If you have any kind of infection, short- or long-term, or if you often get infections. Tell your doctor immediately if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection. If you have had tuberculosis, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. Section 4 POSSIBLE SIDE EFFECTS Possible serious side effects include serious infections and allergic (hypersensitivity) reactions, that may, in a small number of cases, be life-threatening If you notice any of the following signs of: …infections, tell your doctor as soon as possible: -fever and chills -mouth or skin blisters -stomach ache -persistent headaches Additional risk minimization: Alert card to advise patients and health care providers that RoActemra increases the risk of getting infections which can become serious if not treated and of the need for timely diagnostic

		and treatment measures on the first signs of infection. This issue is also addressed in the SmPC, PIL and educational material.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Identified risks		
Complications of diverticulitis (including GI perforation)	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	Routine risk minimization by means of labelling: SPC Section 4.4 Special warnings and precautions for use Complications of diverticulitis Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with RoActemra in RA (see section 4.8). RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation. SPC Section 4.8 Undesirable effects Gastrointestinal Perforation During the six month controlled trials, the incidence of gastrointestinal perforation was 0.26 events per 100 pt-yrs with tocilizumab therapy. In the all exposure population, the overall rate of gastrointestinal perforation was 0.28 events per 100 pt-yrs. Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistula, and abscess. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Take special care with RoActemra If you have had intestinal ulcers or diverticulitis, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.

		Additional risk minimization: Alert card to advise patients and health care providers that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated and of the need for vigilance with respect to signs and symptoms of potential complications of diverticulitis to ensure timely and appropriate diagnostic measures and treatment Information for prescribers, patients and infusion nurses
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Identified risks		
Serious hypersensitivity	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme (see Section 2.3.1) • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	Routine risk minimization by means of labelling: SPC Section 4.4 Special warnings and precautions for use Hypersensitivity reactions Serious hypersensitivity reactions have been reported in association with infusion of RoActemra in approximately 0.3% of RA patients (see section 4.8). A patient with a previous infusion reaction and premedicated with steroids and antihistamines experienced a fatal anaphylactic reaction during a subsequent treatment with RoActemra in the post marketing setting. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with RoActemra. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of RoActemra should be stopped immediately and RoActemra should be permanently discontinued. SPC Section 4.8 Undesirable effects Infusion reactions In the 6-month controlled trials, adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin

		reactions (rash, urticaria). These events were not treatment limiting. The rate of anaphylactic reactions (occurring in a total of 6/3778 patients) was several fold higher with the 4 mg/kg dose compared to the 8 mg/kg dose.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Identified risks		
Serious hypersensitivity (cont'd)		SPC Section 4.8 Undesirable effects / Infusion reactions (cont'd) Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 13 out of 3778 patients (0.3%) treated with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). The safety profile in post marketing experience is consistent with clinical trial data with the exception of a case of a fatal anaphylactic reaction that has been reported during tocilizumab treatment (see section 4.4). sJIA: Infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12 week controlled phase, 4% of patients from the tocilizumab group experienced events occurring during infusion. On event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment. In the 12 week controlled phase, 16% of patients in the tocilizumab group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the tocilizumab group, the events included, but were not limited to rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious. Clinically significant

		hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (<1%) treated with tocilizumab during the controlled and open label clinical trial. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Take special care with RoActemra If you experience allergic reactions such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash during or after the infusion, then tell your doctor immediately. Section 4 POSSIBLE SIDE EFFECTS Possible serious side effects include … and allergic (hypersensitivity) reactions, that may, in a small number of cases, be life-threatening. If you notice any of the following signs of: allergic reactions during or after infusion, tell your doctor immediately: - difficulty with breathing or light-headedness - rash, itching, hives, swelling of the lips. Common side effects: …and serious allergic (hypersensitivity) reactions. Additional risk minimization: Information for prescribers, patients and infusion nurses
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks Neutropenia	• Study to address mechanism of neutrophil reduction • Routine pharmacovigilance • Guided Questionnaire for events of special interest will collect neutrophil data in cases of serious infection • Ongoing clinical trial programme (see Section 2.3.1) • Regular review by Roche Pharmacoepidemiology Board	Study ML25243 Routine risk minimization by means of labelling: SPC section 4.4 Special warnings and precautions for use In RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2. In sJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see section 4.2.

SPC section 4.2 Posology and method of administration

Dose adjustments due to laboratory abnormalities (see section 4.4)

Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/L)	Action
ANC >1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases >1 x 10^9/ l resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC <0.5	Discontinue RoActemra

SPC section 4.4 Special warnings and precautions for use

Haematological abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

Caution should be exercised when considering initiation of RoActemra treatment in patients with a low neutrophil or platelet count (i.e. ANC < 2 x 10^9/ l or platelet count below 100 x 10^3/ µl). In patients with an ANC < 0.5 x 10^9/ l or a platelet count < 50 x 10^3/ µl treatment is not recommended.

In RA patients, eutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2.

In sJIA patients, neutrophils and platelets should be monitored at the time of the second infusion and thereafter according to good clinical practice, see section 4.2.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
Neutropenia (cont'd)		SPC Section 4.8 Undesirable effects/Laboratory evaluations *Haematological abnormalities* *Neutrophils* In the 6-month controlled trials, decreases in neutrophil counts below 1 x

		10^9/ l occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to <0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC <1 x 10^9/ l did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/ l were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs. There was no clear association between decreases in neutrophils and the occurrence of serious infections. During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials. sJIA: During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below 1 x 109/l occurred in 7% of patients in the tocilizumab group, and in no patients in the placebo group. In the ongoing open label extension phase, decreases in neutrophil counts below 1 x 10^9/l, occurred in 15% of the tocilizumab group. There was no clear relationship between decreases in neutrophils below 1 x 10^9/l and the occurrence of serious infections. Patient Information Leaflet Section 4 POSSIBLE SIDE EFFECTS Common side effects: … low white blood counts shown by blood tests (neutropenia, leucopenia)
Thrombocytopenia	• Routine pharmacovigilance • Ongoing clinical trial programme (see Section 2.3.1) • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling: SPC section 4.4 Special warnings and precautions for use In RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2. In sJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see section 4.2. SPC section 4.2 Posology and method of administration <u>Dose adjustments due to laboratory abnormalities (see section 4.4)</u> Low platelet count

Laboratory Value (cells x 10^3/ µl)	Action
50 to 100	Interrupt

			RoActemra dosing When platelet count > 100 x 10^3/ µl resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
			<50 Discontinue RoActemra
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)	
Potential risks			
Thrombocytopenia (cont'd)		SPC section 4.4 Special warnings and precautions for use *Haematological abnormalities* Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8)… Caution should be exercised when considering initiation of RoActemra treatment in patients with a low neutrophil or platelet count (i.e. ANC < 2 x 10^9/ l or platelet count below 100 x 10^3/ µl). In patients with an ANC < 0.5 x 10^9/ l or a platelet count < 50 x 10^3/ µl treatment is not recommended. Neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2 . SPC Section 4.8 Undesirable effects *Haematological abnormalities* *Platelets* In the 6-month controlled trials, decreases in platelet counts below 100 x 10^3/ µl occurred in 1.7% of patients on tocilizumab 8 mg/kg plus DMARDs compared to <1% on placebo plus DMARDs. These decreases occurred without associated bleeding events. During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials. In sJIA: During routine laboratory monitoring in the 12 week controlled phase, 3% of patients in the placebo group and 1% in	

<table>
<tr><td></td><td></td><td>the tocilizumab group had a decrease in platelet count to ≤100 x 103/µl.

In the ongoing open label extension phase, decreases in platelet counts below 100 x 103/µl, occurred in 3% of patients in the tocilizumab group, without associated bleeding events.</td></tr>
<tr><td>Safety Concern</td><td>Proposed Pharmacovigilance Activities (Routine and Additional)</td><td>Proposed Risk Minimisation Activities (Routine and Additional)</td></tr>
<tr><td>Potential risks</td><td></td><td></td></tr>
<tr><td>Elevated hepatic transaminases</td><td>• Routine pharmacovigilance
• Guided Questionnaire (post-marketing data) to collect information on serious hepatic events
• Ongoing clinical trial programme
• Regular review by Roche Pharmacoepidemiology Board
• Nature and frequency of hepatic events representing potential clinical manifestations of increased transaminase levels will be monitored in the registry studies:
o US claims database
o EU registries (BSRBR, ARTIS, RABBIT)</td><td>Routine risk minimization by means of labelling:
SPC section 4.4 Special warnings and precautions for use
In RA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, RoActemra treatment should be interrupted.

In sJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice, see section 4.2.

SPC section 4.2 Posology and method of administration
<u>Dose adjustments due to laboratory abnormalities (see section 4.4)</u>
Liver enzyme abnormalities
<table>
<tr><td>Laboratory Value</td><td>Action</td></tr>
<tr><td>>1 to 3 x Upper Limit of Normal (ULN)</td><td>Dose modify concomitant MTX if appropriate
For persistent increases in this range, reduce RoActemra dose to 4 mg/kg or interrupt RoActemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised
Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate</td></tr>
<tr><td>>3 to 5 x ULN (confirme</td><td>Interrupt RoActemra dosing until <3 x ULN</td></tr>
</table>
</td></tr>
</table>

	d by repeat testing, see section 4.4).	and follow recommendations for > 1 to 3 x ULN (described above) For persistent increases >3 x ULN, discontinue RoActemra
	>5 x ULN	Discontinue RoActemra

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
Elevated hepatic transaminases (cont'd)		SPC section 4.4 Special warnings and precautions for use *Active hepatic disease and hepatic impairment* Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases (see section 4.8), therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see Sections 4.2 and 4.8). *Hepatic transaminase elevations* In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment, without progression to hepatic injury (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. When clinically indicated, other liver function tests including bilirubin should be considered. Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated ALT or AST >1.5 x ULN. In patients with baseline ALT or AST >5 x ULN, treatment is not recommended. In RA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations >3–5 x ULN, confirmed by repeat testing, RoActemra treatment should be interrupted. Once the patient's hepatic transaminases are

		below 3 x ULN, treatment with RoActemra may recommence at 4 or 8 mg/kg. In sJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice, see section 4.2.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
Elevated hepatic transaminases (cont'd)		SPC section 4.8 Undesirable effects *Hepatic transaminase elevations* During the 6-month controlled trials transient elevations in ALT/AST >3 x ULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg tocilizumab plus DMARDs compared to 1.5% of patients on placebo plus DMARDs. The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST >5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials. During the double-blind controlled period, the incidence of indirect total bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg tocilizumab + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of >1 to 2 x ULN and 0.4% had an elevation of >2 x ULN. sJIA: During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST ≥3 x ULN occurred in 5% and 3% of patients, respectively, in the tocilizumab group, and 0% in the placebo group. In the ongoing open label extension phase, elevation in ALT or AST ≥3 x ULN occurred in 12% and 4% of

		patients, respectively, in the tocilizumab group. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Take special care with RoActemra - If you have liver disease, tell your doctor. Before you use RoActemra, your doctor may examine your liver function. Section 4 POSSIBLE SIDE EFFECTS Common side effects: .abnormal liver function tests (increased transaminases)
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
Immunogenicity	• Routine pharmacovigilance • Ongoing clinical trial programme (see Section 2.3.1) • Post-approval commitment to collect antibody titre data on all patients who experience immune-mediated AEs and those who have had a dosing holiday • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling: SPC section 4.8. Undesirable effects *Immunogenicity* A total of 2876 patients have been tested for anti-tocilizumab antibodies in the controlled clinical trials. Of the 46 patients (1.6%) who developed anti-tocilizumab antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients developed neutralising antibodies. sJIA: All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal. The incidence of anti-tocilizumab antibody formation might be underestimated because of interference of tocilizumab with the assay and higher drug concentration observed in children compared to adults.
Elevated lipids	• Study WA19923 evaluating the effects of IL-6 receptor blockade with tocilizumab (TCZ) on lipids, arterial stiffness, and markers of atherogenic risk in patients with moderate to severe active RA • Routine pharmacovigilance • Ongoing clinical trial programme (see Section 2.3.1) • Guided Questionnaires on implications of elevated lipids: ischaemic cardiovascular events (e.g., MI/acute coronary syndrome) and implications of elevated lipids: cerebrovascular events (e.g., stroke) • Regular review by Roche Pharmacoepidemiology	Routine risk minimization by means of labelling: SPC section 4.4 Special warnings and precautions for use *Lipid parameters* Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with tocilizumab (see section 4.8). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents. Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

	Board • Rate of clinical events potentially related to atherogenesis (e.g. angina, MI, cerebrovascular accident) as a potential clinical manifestation of increased lipid levels will be monitored in the registry studies. The nature and rate of such events will be monitored and evaluated on the basis of reports to the: o Routine pharmacovigilance o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	Cardiovascular Risk RA patients have an increased risk for cardiovascular disorders and should have risk factors (eg. hypertension, hyperlipidaemia) managed as part of usual standard of care. SPC section 4.8 Undesirable effects *Lipid parameters* During the six month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol ≥6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to ≥4.1 mmol/ l. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
Elevated lipids (cont'd)		During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled clinical trials. sJIA: During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol >1.5 x ULN to 2 x ULN occurred in 1.5% of the tocilizumab group and in 0% of placebo group. Elevation in LDL >1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the tocilizumab group, and in 0% of the placebo group. In the ongoing open label extension phase, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled phase data. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Take special care with RoActemra If you have cardiovascular risk factors such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra. Section 4 POSSIBLE SIDE EFFECTS Very common side effects…high cholesterol levels… Uncommon side effects…high blood fat

		(triglycerides)
Malignancies	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme (see Section 2.3.1) • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	Routine risk minimization by means of labelling: SPC section 4.4 Special warnings and precautions for use *Malignancy* The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy. SPC section 4.8 Undesirable effects *Malignancies* The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.
Demyelinating disorders	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme (see Section 2.3.1) • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	Routine risk minimization by means of labelling: SPC section 4.4 Special warnings and precautions for use *Neurological disorders* Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
CYP450 enzyme normalisation	• Routine pharmacovigilance • Ongoing clinical trial programme (see Section 2.3.1) • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling: SPC section 4.5 Interaction with other medicinal products and other forms of interaction The expression of hepatic CYP450 enzymes is suppressed by the cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as tocilizumab, is introduced. *In vitro* studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression. Tocilizumab normalises expression of these enzymes. When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or

		benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
CYP450 enzyme normalisation		Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Using other medicines Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. You should tell your doctor if you are using medicines containing any of the following active substances: • atorvastatin, used to reduce cholesterol levels • calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure • theophylline, used to treat asthma • warfarin, used as a blood thinning agent • phenytoin, used to treat convulsions • ciclosporin, used to suppress your immune system during organ transplants • benzodiazepines (e.g. temazepam), used to relieve anxiety
Missing Information		
Mortality in the Japanese PMS (RA indication)	• Routine pharmacovigilance • Regular review by Roche • Semiannual review with PSURs (more frequently as warranted) – frequency to be re-examined after PSUR No. 4 • Pharmacoepidemiology Board	The last Japanese PMS safety data for the RA indication has been updated on Chugai's website up to 3 August 2010, which was the last day the PMS was in effect for the RA indication. The data are available to prescribers and patients in Japan.
Elderly patients	• Routine pharmacovigilance • Ongoing clinical trial programme (see Section 2.3.1) • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	Routine risk minimization by means of labelling SPC section 4.2 Posology and Method of Administration Special populations *Elderly Patients* No dose adjustment is required in patients aged 65 years and older.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing information		

Paediatric patients	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board • On-going Study WA18221 (sJIA) where different dose interval strategies will be investigated in the longterm extension. In addition, investigations into dose reductions / treatment interruptions will be reported in upcoming PSURs. • On-goingStudy WA19977 (pJIA)	Routine risk minimization by means of labelling: SPC Section 4.2 Posology and Method of Administration Special Populations *Paediatric Patients* The safety and efficacy of RoActemra in patients below 2 years of age has not been established. No data are available. The recommended posology is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA RoActemra is not recommended for use in patients under 2 years of age..
Effects during pregnancy	• Routine pharmacovigilance • Ongoing clinical trial programme (see Section 2.3.1) • Regular review by Roche Pharmacoepidemiology Board • Registry study with OTIS • Pregnancy data from BSRBR and RABBIT	Routine risk minimization by means of labelling: SPC section 4.6 Pregnancy and lactation Pregnancy There are no adequate data from the use of tocilizumab in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown. Women of childbearing potential have to use effective contraception during (and up to 3 months after) treatment. RoActemra should not be used during pregnancy unless clearly necessary. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Pregnancy and breast-feeding Talk to your doctor if you are pregnant, may be pregnant, intend to become pregnant or if you are breast-feeding. Women of childbearing potential must use effective contraception during and up to 3 months after treatment. RoActemra should not be used during pregnancy unless clearly necessary.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)

Missing information		
Effects during pregnancy (cont'd)		Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA (cont'd) It is not known whether RoActemra is excreted in breast milk. If you are a nursing mother, you should stop breast-feeding if you are to be given RoActemra. Before starting breast-feeding, your last treatment with RoActemra should be at least 3 months ago.
Hepatic impairment	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling: SPC section 4.2 Posology and Method of Administration. Special populations *Hepatic Impairment* RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made. SPC section 4.4 Special warnings and precautions for use *Active hepatic disease and hepatic impairment* Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8). SPC section 5.2 Pharmacokinetic properties Special populations *Hepatic impairment:* No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Take special care with RoActemra If you have liver disease, tell your doctor. Before you use RoActemra, your doctor may examine your liver function.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing information		
Renal impairment	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling SPC section 4.2 Posology and Method of Administration Special populations *Renal Impairment* No dose adjustment is required in patients with mild renal impairment.

		RoActemra has not been studied in patients with moderate to severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients. SPC section 5.2 Pharmacokinetic properties <u>Special populations</u> *Renal Impairment:* No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 ml/min and ≥ 50 ml/min) did not impact the pharmacokinetics of tocilizumab. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Take special care with RoActemra If you have moderate to severe kidney function problems, your doctor will monitor you.
Combination with biologics	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	Routine risk minimization by means of labelling: SPC section 4.4 Special warnings and precautions for use *Combination with TNF antagonists* There is no experience with the use of RoActemra with TNF antagonists or other biological treatments for RA or sJIA. RoActemra is not recommended for use with other biological agents. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA Using other medicines Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing information		
Vaccinations	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board • Plans for dedicated study under discussion	Routine risk minimization by means of labelling: SPC section 4.4 Special warnings and precautions for use *Vaccinations* Live and live attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. It is recommended that all patients, particularly sJIA patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to

	initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. Patient Information Leaflet Section 2 BEFORE YOU USE ROACTEMRA If you have recently got or are planning to get vaccinated, tell your doctor. Certain types of vaccines should not be given while receiving RoActemra. Dedicated vaccination study (NA25256) dedicated vaccination study, with eight week titre data to be submitted in March 2012 followed by a CSR in September 2012.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation and pharmacovigilance activities were required:

- Physician Information which contain the following key elements: Diagnosis of Macrophage Activation Syndrome in sJIA patients and recommendations for dose interruptions.
- Report on the exploratory objectives surrounding the proposed alternative dosing schedule in Part III of study WA18221
- Provide updates on the following registries, based on available data (BSRBR, ARTIS, RABBIT, ENTIS, Paediatric Rheumatology in Europe Society, Planned Arthritis Research Council paediatric biologicals registry)
- The MAH will perform a study to investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients.
- The patient alert card (see model in attachment) as part of the patient information pack (see Annex II) has been updated in order to cover the risks associated to sJIA.

1.3.5. PSURs

The Marketing Authorisation Holder will submit PSURs at 6-monthly intervals due to the limited available safety data in sJIA patients.

1.3.6. User consultation

RoActemra in combination with MTX is currently approved for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients. The present application concerns an extension of the indication for the treatment of systemic juvenile idiopathic arthritis in children 2 years of age and older.

The applicant has provided a justification why no new user consultation of the package leaflet is needed as a result of this extension application. However, the CHMP is of the opinion that some changes have been made related to the SmPC and the package leaflet including changes to the safety messages. Therefore a user testing on this amended version of the PL will be performed.

2. Overall conclusion and benefit-risk assessment

Benefits

Beneficial effects

The following beneficial effects were investigated in the clinical studies with tocilizumab:

Treatment of symptom and signs: Endpoint for evaluating this benefit is the response for JIA ACR30 and absence of fever. This response was met in 85.3% (95% CI 77.3 – 93.3%) of the total tocilizumab treated population compared to 24.3% (95% CI 10.5 – 38.1%) in the placebo population. More stringent criteria (JIA ACR50, JIA ACR70, JIA ACR90) confirm this effect.

Correction of anaemia: Anaemia is caused by a combination of factors in long standing disease. It could therefore be regarded as a surrogate of disease activity although it has not been validated for this use. Of those placebo treated patients that had anaemia at baseline 2/29 (6.9%, 95% CI 0.0 – 16.1%) had normal haemoglobin at week 12. In the total tocilizumab treated population 40/50 (80%, 95% CI 68.9 – 91.1) had normal haemoglobin at week 12.

Decrease of concomitant corticosteroid therapy: The protocol allowed reduction of corticosteroid dose if JIA ACR70 response was met at weeks 6 or 8. One/31 (3.2%, 95% CI 0.0 – 9.4%) placebo patient and 17/70 (24.3%, 95% CI 14.2 – 34.3) tocilizumab treated patients reduced their oral corticosteroid dose by 20% to week 12 without experiencing a flare.

Remission of disease symptoms: The most stringent criterion is a JIA ACR90 response, this was met by 2/37 (95%CI 0.0 – 12.7%) in the placebo group and 28/75 (95% CI 26.4 – 48.3%) in the total tocilizumab group.

Functional improvement: For the assessment of functional improvement in daily live CHAQ-DI was used. 58/75 (77.3%, 95% CI 67.9 – 86.8%) TCZ patients and 7/37 (18.9%; 95%CI 6.3 – 31.5%) placebo patients had a minimally important improvement (0.13) in CHAQ-DI score from Baseline to Week 12.

Uncertainty in the knowledge about the beneficial effects

With regard to these investigated beneficial effects, the following observations were made:

Treatment of symptom and signs: Sources of uncertainty are related to the population recruited and the rather pronounced effect on CRP and fever with the potential of unblinding. However, given the results of the conducted sensitivity analyses and the magnitude of the treatment effect there is little uncertainty for these beneficial effects. Even a halving of the effect size would be regarded as clinical meaningful in this patient population if statistical significance were demonstrated. It is interesting to note that the physician component and the parent component appear to be diverging in the sense that in the placebo group physician evaluation is stating improvement over time whereas the parent evaluation appears to indicate no large change in disease severity.

Correction of anaemia: Correction of anaemia is not an accepted surrogate for disease activity in sJIA. However for a condition with chronic inflammation and ensuing anaemia this endpoint constitutes a valuable confirmation of the beneficial effect. Since this is a rather objective endpoint uncertainties mainly relate to the possibility of transfusion in extreme cases. It is difficult to define clinically meaningful changes. LLN is an obvious choice for a cut-off.

Decrease of concomitant corticosteroid therapy: In a blinded trial this is considered clinically as a very relevant endpoint. Of note, any changes from baseline could result in increased disease activity and

would therefore impact on the primary efficacy endpoint. Source of variability are mainly compliance with the treatment regimen.

Remission of disease symptoms: Similarly to the above "symptoms and signs" evaluation main sources of uncertainty is the population recruited into the trial and the potential for unblinding. From the supportive data the remarkable increase over a longer time period increases the confidence in the 12 week data.

Functional improvement: Uncertainties mainly relate to the term "minimally important improvement". Robustness of the effect could be questioned. The effect size and the conditions under which it was obtained are not considered to be a relevant source of variation.

In addition, there are some potential beneficial effects of tocilizumab in systemic juvenile idiopathic arthritis, which would however require additional data either long-term of with larger sample sizes:

Prevention of MAS, decrease in mortality: This would be a clear-cut endpoint requiring a large sample size. From the obtained data no judgement can be made. Further data, e.g. from registries will be collected to obtain a larger sample size. Uncertainties relate to the difficulties in diagnosis, the multiple triggering mechanisms and the multi-modal treatment. Furthermore, an investigation of the primary or secondary influence of tocilizumab in the risk for developing MAS will be addressed in the post-marketing observation period, within the context of the ongoing Part II and Part III of study WA18221 as detailed in the RMP.

Prevention of structural damage: This would be the most important beneficial effect as regards the arthritis component of the disease. No long term data are available therefore it is uncertain whether this beneficial effect can be obtained. Data from adult rheumatoid arthritis make it more likely that also a beneficial effect can be demonstrated.

Preservation of bone integrity: sJIA is associated with osteoporosis but the role of IL-6 in bone metabolism is not well defined and the current data are conflicting. In order to dissect the potential detrimental effects of IL-6R inhibition on the bone long term data are needed evaluating e.g. the effect of therapy on bone mineral density. Data on concomitant corticosteroid use are needed. The MAH is going to address this with the long term data of WA18221 (phase II and III) as detailed in the RMP.

Resumption of growth and physical development: This highly relevant beneficial effect requires long term data that are not available but will be collected in the long term extension of WA18221 as detailed in the RMP.

Remission of disease: Based on the available data it is uncertain whether inhibition of IL-6R is necessary long-term or whether remission can be obtained without treatment with tocilizumab after a defined treatment phase. The MAH is planning to address this in part with the investigation of different dosing regimen in the extension phase (Part III of study WA18221 will assess the long-term durability and magnitude of the tocilizumab efficacy response in patients with sJIA including meeting the definition of inactive disease and clinical remission) as mentioned in the RMP.

Decreased inflammatory burden, Prevention of amyloidosis: Amyloidosis is a rare complication nowadays. From the demonstrated effect of tocilizmab treatment on SAA there is little doubt that amyloidosis could be prevented if it were still a major clinical problem. More difficult is the question whether a "decreased inflammatory burden" will decrease the cardiovascular risk in the future.

Risks

Unfavourable effects

Overall, the qualitative safety profile of tocilizumab in children as demonstrated in the data for systemic idiopathic arthritis appears to be generally comparable to data on rheumatoid arthritis in adults. The following unfavourable effects were observed:

Infection: Infections are in general increased in tocilizumab treated patients. Serious infections occurred with increasing incidence in the longer term studies. For the long term extension of the pivotal trial SAE infections and infestations are reported with 11.3 per 100 patient years. The main confounding factor is concomitant corticosteroid use. Based on the type and severity of infection observed thus far, with the exception of bacterial arthritis and pneumonia, there is no specific concern. Bacterial arthritis has been reported to be more common in adult patients with rheumatoid arthritis, whether this is the case in children is unknown. The SmPC provides adequate guidance under "Special warnings and precautions for use"; also the educational programme addresses this safety aspect.

Anaphylaxis: Life threatening anaphylaxis has occurred in one patient in the placebo controlled part. This is a medically highly significant event. The SmPC as well as the educational programme provide adequate guidance on serious hypersensitivity reactions and their management.

Neutropenia: Neutropenia is clearly increased in tocilizumab treated patients, it is reversible on discontinuation and not unfavourable per se, it is the assumed association with infection that defines its role as unfavourable. Relevant information is provided in the SmPC and the educational programme.

AST/ALT/bilirubin elevation: In general, the medical significance of the observed elevation of transaminases and bilirubin is unclear. Guidance for monitoring of these laboratory changes is provided in the SmPC.

Thrombocytopenia: Thrombocytopenia has been observed, which could be a medically important event if associated with bleeding. The SmPC indicated these aspects.

Hypercholesterolaemia: Hypercholesterolaemia is a cardiovascular risk factor. Small increments are noted for the total population, for individuals with a high baseline this increase could become relevant. Guidance for monitoring is provided in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

As established for tociliziumab for the adult indication, there are areas with uncertainty about the unfavourable effects. These are addressed in the SmPC and through risk minimisation activities described in the risk management plan, as appropriate. Regarding the above indicated unfavourable effects observed in the paediatric studies to support the present extension application, the following observations are made:

Infection: The uncertainties relate to the unknown potential for serious opportunistic infections and the unknown incidence of fatal infections. This issue is closely related to MAS (see below) and to neutropenia.

Anaphylaxis: It is an unfavourable effect that cannot be predicted based on pre-clinical data. So far immunogenicity appears not to be a common occurrence but this may change with different background therapy e.g. reduced corticosteroid use. Uncertainties relate to the difficulty in diagnosing hypersensitivity reactions, they may in fact be underdiagnosed, and defining the most appropriate strategy for identifying patients that should be discontinued from treatment.

Neutropenia: Neutropenia is by general medical knowledge expected to be associated with infection. However, this relationship has not been unequivocally been established for tocilizumab. At present it is regarded that there is a high likelihood of a causal relationship between severe neutropenia and infection, however there is no proof from the data.

AST/ALT/bilirubin elevation: Uncertainties relate to the unknown consequences of long-time mild to moderate transaminase elevations. It is unknown whether a mere shift in baseline, that appears likely from the provided data, may have long-term consequences.

Thrombocytopenia: The occurrence is relatively well described however, the risk of haemorrhage is uncertain, but not regarded as high considering the data in paediatric population so far.

Hypercholesterolaemia: The increase in cardiovascular risk that would be attributable to long term cholesterol increase is unknown.

Further to these areas of uncertainties, there are other potential unfavourable effects:

MAS/HLH: MAS can be the consequence of insufficient treatment, but can also be triggered by infection and potentially by certain drugs. The occurrence of MAS in the main trial supporting the sJIA indication and the extension studies appears to compare favourably to literature data. However, the reported incidences cover a wide range and a clear picture could only be generated by a long term comparative trial which is not feasible. Triggering of MAS could also follow hypersensitivity reactions and infections, AE that could become more frequent with longer standing IL-6 receptor blockade. This safety aspect has therefore been added to the SmPC and to the educational programme.

Pneumothorax: From the mechanism of action the causal relationship of pneumothorax to therapy is uncertain. One possible pneumothorax with fatal outcome was observed. Considering the incidence of pneumothorax in general it is less likely that this is a chance event, although this cannot be excluded.

Hypogammaglobulinaemia: This was reported as an AE in a Japanese study, there are also cases flagged in the WA18221 study report. Hypogammaglobulinaemia is associated with an increased risk of infections. Uncertainty exists about the rate of occurrence long term because of lack of long term study data. If confirmed this conveys with a higher likelihood and increased risk of infections. This will be followed through routine pharmacovigilance activities and additional surveillance through registries and studies as detailed in the RMP.

Masking of infectious complications/ "false negative CRP": Efficient IL-6R blockade theoretically inhibits the acute phase response to infection, CRP for example could be a less reliable marker and fever response would also be attenuated. There is uncertainty whether these observed effects lead to a delay in the diagnosis of infections. In the end severity of infection would be a "composite" of the infection per se and the delay of diagnosis. The SmPC as well as the educational programme provide respective guidance.

Vaccine inefficacy: Interventions in components of the immune system harbour the risk of a decrease of wanted immunogenicity. In the absence of specific data with tocilizumab a dedicated study of the effects of TCZ on vaccination to evaluate the effects of tocilizumab on vaccination in subjects with active rheumatoid arthritis receiving background methotrexate is currently planned as detailed in the RMP.

Balance

Importance of favourable and unfavourable effects

There is a high unmet medical need for the treatment of patients with sJIA. The observed responses as regards symptoms and signs are very important and constitute the primary goal of any treatment. The strength of the data lies in an effect that could be regarded as remission in a considerable fraction of patients. Reduction in corticosteroid dose is another very important goal of treatment for the prevention of corticosteroid induced side effects. Correction of anaemia is of lesser importance but may be indicative of an influence on disease activity overall. Functional improvement by itself is of lesser importance.

The most important unfavourable effects are infections and neutropenia because of the risk of permanent consequences (e.g. joint destruction). As part of the pharmacovigilance activities, anaphylaxis needs to be monitored if the incidence of severe/serious reactions increases. Transaminase elevations are of importance because of the involvement of a vital organ and the unknown long term consequences. Thrombocytopenia without bleeding is of lesser importance and hypercholesterolaemia is considered less important for short term considerations, but needs to be monitored for long term benefit/risk considerations. The SmPC and the Risk Management Plan adequately addresses these safety-related topics. In addition, a dedicated educational programme provides information and guidance. In addition, the MAH will perform a study to investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients as detailed in the RMP.

Benefit-risk balance

The demonstrated beneficial effects on symptoms and sign of disease and associated functional improvement as well as the possibility to reduce corticosteroid treatment as demonstrated in the pivotal trial outweigh the most important risk of increase in infections, risk of neutropenia and transaminase elevation.

Discussion on the benefit-risk assessment

The benefit risk assessment is based on the short term data in a controlled setting and longer term uncontrolled data with a small sample up to one year. These data are considered appropriate based on a high unmet medical need in a disease with limited treatment options.

Overall, the efficacy as demonstrated with these data is considered of high clinical relevance. Because of the small sample size and the short follow-up there are uncertainties around the incidence of severe events such as anaphylaxis, serious infections, opportunistic infections and long term effect on the liver as well as the beneficial effect on disease activity. Nevertheless, these uncertainties do not offset the demonstrated beneficial effects and the potential beneficial effects on disease activity and long term outcome that may even be the true, although not obtainable, indicators of benefit for the patient. It is noted that the appropriate dose in the long term setting needs further monitoring; the applicant will investigate different dosing strategies in the ongoing extension of the pivotal trial as detailed in the RMP, which is deemed acceptable. The MAH will also perform a study to investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients as detailed in the RMP.

It is necessary to generate long term data through a systematic collection of as many patient data as possible in a comprehensive fashion e.g. under registry conditions. Given that sJIA may be a life long disease in a subset of patient and given that a number of off label treatments are used in clinical

practice it is important to follow these patients long term, in particular because disease complications that are usually reserved to the adult domain may become important, e.g. accelerated cardiovascular disease. The applicant will provide updates from several European registries including BSRBER, ARTIS and RABBIT.

The following indication is therefore agreed for section 4.1 of the SmPC:

"RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX".

3. Conclusion

On 19 May 2011 the CHMP considered this following variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II Labelling and Package Leaflet.

Furthermore, the CHMP reviewed the data submitted by the MAH taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considered the indication to be new and that it is held to bring a significant clinical benefit in the absence of existing therapies (see appendix).