25 April 2013
EMA/393130/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0026

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd submitted to the European Medicines Agency on 11 June 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
RoActemra	tocilizumab	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to extend the indication of tocilizumab for the treatment in combination with methotrexate (MTX) of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Sections 1, 2, 3, 4 and 6 of the Package Leaflet were proposed to be updated in accordance.

In addition, the MAH took the opportunity to include minor editorial changes throughout the PI.

Furthermore, the PI is being brought in line with the latest QRD template.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: János Borvendég

1.2. Steps taken for the assessment

Submission date:	11 June 2012
Start of procedure:	24 June 2012
Rapporteur's preliminary assessment report circulated on:	17 August 2012
Co-Rapporteur's preliminary assessment report circulated on:	15 August 2012
Joint Rapporteurs' assessment report circulated on:	13 September 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 September 2012
MAH's responses submitted to the CHMP on:	16 November 2012
Joint Rapporteurs' assessment report circulated on:	19 December 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	17 January 2013
MAH's responses submitted to the CHMP on:	21 February 2013
Joint Rapporteurs' assessment report circulated on::	27 March 2013
Joint Rapporteurs' updated assessment report circulated on:	15 April 2013
CHMP opinion:	25 April 2013

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006 as amended, the application included an EMA decision (P/277/2011) for the following condition(s):

- Treatment of autoimmune arthritis

on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2. Scientific discussion

2.1. Introduction

Tocilizumab (RoActemra) is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against the soluble and membrane-bound interleukin 6 receptor (sIL-6R and mIL-6R).

RoActemra is authorised 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 and for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older 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 both indications for adult RA patients, RoActemra can be given as in combination with MTX or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Juvenile idiopathic arthritis (JIA) is arthritis of at least 6 weeks duration of unknown aetiology that begins in children less than 16 years old. Although less common than rheumatoid arthritis (RA) in adults, JIA is one of the most common systemic autoimmune systemic autoimmune diseases in children and adolescents. According the ILAR scheme JIA is classified in 7 categories

Figure 1. Frequency, age at onset and gender distribution of ILAR categories of JIA

Subset	Frequency [a]	Onset Age	Gender Ratio
Systemic JIA	4% - 17%	Throughout childhood	F = M
Oligoarthritis	27% - 56%	Early childhood; peak at 2-4 years	F >>> M
RF-positive polyarthritis	2% - 7%	Late childhood or adolescence; peak at 10-14 years	F >> M
RF-negative polyarthritis	11% - 28%	Biphasic distribution; early peak at 2-4 years and later peak at 6-12 years	F >> M
Enthesitis-related arthritis	3% - 11%	Late childhood or adolescence	M >> F
Psoriatic arthritis	2% - 11%	Biphasic distribution; early peak at 2-4 years and later peak at 9-11 years	F >> M
Undifferentiated Arthritis	2% - 15%		

[a] Reported frequencies refer to percentage of all juvenile idiopathic arthritis.
F: female; M: male; RF: rheumatoid factor.

In the present submission, the polyarticular JIA (pJIA) population studied in the phase III clinical study WA19977 consists of three subsets: rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, and extended oligoarthritis.

The current submission aims to extend the indication of RoActemra to the treatment in combination with methotrexate (MTX) of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX.

2.2. Clinical aspects

2.2.1. Introductions

This application is supported by Part I data (16-week active tocilizumab treatment lead-in period) and Part II (24-week randomized double-blind placebo-controlled withdrawal period) from the pivotal Phase III study WA19977 and two supportive studies: studies MRA318JP and MRA319JP.

GCP

The clinical trials were performed in accordance with GCP as claimed by the Applicant. The Applicant 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.

Table 1. Tabular overview of clinical studies

Study	Design	Patients
Pivotal phase III trial to evaluate efficacy and safety of TCZ in patients with pJIA:		
WA19977	Two-year study in three parts: Part I: 16-week open-label TCZ therapy: BW ≥30 kg: 8 mg/kg TCZ IV q4w BW < 30 kg: 8 or 10 mg/kg TCZ IV q4w Part II: 24-week double-blind, placebo-controlled, randomized withdrawal period in patients achieving JIA ACR30 response at week 16 of Part I; same TCZ dose as in Part I or placebo Part III: 64-week open-label extension (ongoing)	Patients with pJIA for at least six months and with at least five active joints; age at screening was 2-17 years. Treated in Part I: N = 188 (8 mg/kg TCZ: n = 153; 10 mg/kg TCZ: n = 35) Treated in Part II: N = 163 (8 mg/kg TCZ: n = 66; 10 mg/kg TCZ: n = 16; placebo: n = 81)
Supportive trials:		
MRA318JP	12-week open-label, single-arm study; TCZ dose 8 mg/kg IV q4w	Japanese patients with pJIA with at least five active joints; age at baseline 3-19 years; N = 19
MRA319JP	Long-term extension of MRA318JP; total TCZ 8 mg/kg IV q4w treatment duration 0.35–3.53 years	Patients who completed MRA318JP: N = 19

2.2.2. Clinical Pharmacology

Data on the PK and PD characteristics of TCZ have been previously submitted as part of the initial MAA and as part of variation II/15 to extend the indication of TCZ to the treatment of sJIA. This submission includes new data in pJIA patients. The TCZ clinical pharmacology program for pJIA was conducted to characterize the PK and PD of TCZ as well as the exposure-efficacy and exposure-safety relationships. These data are presented below and are based on studies WA19977, MRA318JP and MRA319JP. Population PK analyses were performed for studies WA19977 and MRA318JP.

2.2.2.1. Pharmacokinetics

Methods of analysis

In Part I of the pivotal study, blood samples for PK (TCZ serum concentrations) and PD (IL-6 and sIL-6R) analysis were collected pre-dose and post-dose (within 15 minutes following the saline flush marking the end of infusion) on Day 1; at the Week 4, 8, and 12; at any time during Weeks 1, 2, 6, and 10; and pre-dose at Week 16. In part II of the study, pre-dose blood samples for PK and PD analysis were collected at the Week 20, 24, 28, 32, 36, and 40 visits, and additional samples were taken at any time during Weeks 18 and 22.

The presence of anti-TCZ antibodies was assessed at baseline (pre-dose on Day 1) and at Week 40. In part II of the study, the visit when JIA ACR30 flare relative to Week 16 had occurred was designated “the flare visit”. At the first visit when the flare definition was met, an additional sample was obtained for assessment of potential anti-TCZ antibodies.

PK Results

Nonlinear mixed effects modeling was used to analyse the serum concentration-time TCZ data collected in study WA19977. The population PK dataset consisted of 2631 TCZ serum concentrations from 188 pJIA patients. The serum concentration-time course for TCZ in patients with pJIA was best described by a two-compartment disposition pharmacokinetic model with parallel first-order and Michaelis-Menten elimination kinetics.

Table 2. Summary of TCZ Pharmacokinetic Exposure Parameters (Study WA19977 PK Population, Part I)

Pharmacokinetic Parameters: Mean ± Standard Deviation (Median, Min-Max)			
	TCZ 10 mg/kg (< 30 kg)	**TCZ 8 mg/kg (< 30 kg)**	**TCZ 8 mg/kg (≥ 30 kg)**
Model-computed	**n = 32**	**n = 30**	**n = 115**
$AUC_{wk12-16}$, µg·day/mL	968 ± 254 (934, 445-1658)	702 ± 218 (712, 336-1239)	1231 ± 361 (1157, 610-2228)
C_{max_wk12}, µg/mL	175 ± 32 (175,108-256)	140 ± 25 (141, 92-187)	182 ± 37 (179,107-341)
C_{min_wk16}, µg/mL	2.35 ± 3.59 (0.88, 0-16.3)	0.95 ± 2.07 (0.09, 0.0-7.7)	7.49 ± 8.20 (4.11, 0.0-36.3)
Observed	**n = 29**	**n = 27**	**n = 113**
C_{wk16}	2.75 ± 4.19 (1.02, 0.0-18.7)	0.98 ± 2.26 (0.0, 0.0-9.06)	7.44 ± 8.48 (4.4, 0.0-39.1)

n: number of patients contributing to summary statistics; AUC: area under the concentration time curve; C_{wk16}: observed predose concentration at week 16; $AUC_{wk12-16}$, C_{max_wk12} and C_{min_wk16} are PK model-computed.

Table 3. Summary of TCZ PK Exposure Parameters by ACR Response Status to Week 16 for All Patients (Part I)

Non-Responders	JIA ACR30	JIA ACR50	JIA ACR70	JIA ACR90
$AUC_{wk12-16}$, µg·day/mL	850±394 (882, 336–1518) n=13	922±401 (917, 336–1890) n=25	1032±387 (1016, 336–1974) n=62	1075±377 (1020, 336–2179) n=128
C_{max_wk12}, µg/mL	156±46 (156, 92–249) n=13	161±40 (171, 92–249) n=25	169±37 (171, 92–264) n=62	171±36 (170, 92–264) n=128
C_{wk16}, µg/mL	2.57±3.95 (0.00, 0.0–10.8) n=11	3.64±5.83 (0.0, 0.0–18.7) n=23	4.43±6.6 (1.38, 0.0–29.7) n=58	5.41±7.39 (2.19, 0.0–31.8) n=122
Responders	**JIA ACR30**	**JIA ACR50**	**JIA ACR70**	**JIA ACR90**
$AUC_{wk12-16}$, µg·day/mL	1113±374 (1052, 431–2228) n=164	1122±371 (1062, 478–2228) n=152	1127±375 (1063, 478–2228) n=115	1143±392 (1063, 556–2228) n=49
C_{max_wk12}, µg/mL	175±37 (173, 105–341) n=164	175±37 (173, 106–341) n=152	176±38 (174, 106–341) n=115	180±43 (175, 107–341) n=49
C_{wk16}, µg/mL	5.81±7.83 (2.34, 0.0–39.1) n=158	5.91±7.89 (2.76, 0.0–39.1) n=146	6.21±8.13 (3.47, 0.0–39.1) n=111	6.11±8.41 (2.43, 0.0–39.1) n=47

Source: std1_a30w_pk_1, std1_a50w_pk_1, std1_a70w_pk_1, and std1_a90w_pk_1.
Mean±SD (median, min–max) is presented; n: represents number of patients contributing to summary statistics; ; $AUC_{wk12-16}$ and C_{max_wk12} were pharmacokinetic model computed; C_{wk16}: observed pre-dose TCZ concentration at Week 16

A trend towards lower exposures in non-responders compared with responders, across JIA ACR30/50/70/90 was observed. This is even more pronounced for JIA ACR30 and JIA ACR50. Comparing the mean PK exposures across non-responders for JIA ACR30/50/70/90, there is a trend towards lower exposures in the least responsive patients (i.e. JIA ACR30 non-responders).

In contrast, when the mean pharmacokinetic exposures were compared across responders for JIA ACR30/50/70/90, there was no trend observed.

Table 4. Summary of TCZ Pharmacokinetic Exposure Parameters by JIA ACR30 Flare Status from Week 16 to Week 40 (Part I and II)

JIA ACR30 Flare Status	Treatment Group		
	10 mg/kg (< 30 kg)	8 mg/kg (< 30 kg)	8 mg/kg (≥ 30 kg)
JIA ACR30 flare: No			
$AUC_{wk36\text{-}40}$, µg·day/mL	1120±185 (1104, 822–1497) n=11	819±215 (851, 498–1202) n=9	1454±522 (1341, 656–2885) n=37
C_{max_wk36}, µg/mL	191±26 (186, 153–237) n=11	151±24 (158, 118–190) n=9	199±50 (202, 113–341) n=37
C_{trough}, µg/mL	3.03±2.62 (2.03, 0.2–7.6) n=10	2.07±3.67 (0.24, 0.0–10.8) n=9	10.76±9.92 (8.14, 0.0–33.2) n=37
JIA ACR30 flare: Yes			
$AUC_{wk36\text{-}40}$, µg·day/mL	2132 — n=1	1008±56 (1008, 968–1047) n=2	1312±342 (1235, 709–2105) n=13
C_{max_wk36}, µg/mL	312 — n=1	172±17 (172, 160–184) n=2	194±37 (196, 119–244) n=13
C_{trough}, µg/mL	15.0 — n=1	1.84±0.85 (1.83, 1.2–2.4) n=2	6.71±7.26 (5.11, 0.1–25.6) n=13

Source: std1_a30f_pk_12.

Mean±SD (median, min–max) is presented unless sample size=1, in which case the single value is presented. n=number of patients contributing to summary statistics. C_{trough}=within-patient mean pre-dose TCZ serum concentration from Week 20 through Week 40. $AUC_{wk36\text{-}40}$ and C_{max_wk36} were model predicted. Patients who withdrew or who took escape medication were classified as having had a flare.

Comparison of PK between pJIA, sJIA and adult RA patients

Table 5. Model Predicted PK Exposure Parameters in pJIA and sJIA Paediatric Patients and in Adult RA Patients

Population	Dose Regimen	C_{max}, µg/mL	C_{min}, µg/mL	AUC_{2weeks} µg·day/mL	AUC_{4weeks} µg·day/mL	Ref
sJIA	8 mg/kg Q2W (≥30 kg)	226±54.5	54.5±20.7	1337±409	NA	[6]
	12 mg/kg Q2W (<30 kg)	263±54.1	60.5±25.5	1346±426	NA	[6]
pJIA Japanese	8 mg/kg Q4W	145±34.7	4.88±4.68 (week 12)	NA	1054± 280 (AUC_{inf} for first dose)	MRA318JP
pJIA	8 mg/kg Q4W (≥30kg)	182± 37	7.49±8.20	NA	1231± 361	WA19977
	10 mg/kg Q4W (<30kg)	175± 32	2.35±3.59	NA	968± 254	WA19977
	8 mg/kg Q4W (<30kg)	140± 25	0.95±2.37	NA	702± 218	WA19977
RA	8 mg/kg Q4W	187±85	8.6±8.9	NA	1417± 613	[CTD Section 1.14.2.2]
	4 mg/kg Q4W	88±41	1.4±1.9	NA	538± 239	[CTD Section 1.14.2.2]

Mean ± SD is reported: Q2W=every 2 weeks; Q4W=every 4 weeks; NA=not applicable, since the dosing interval is 2 weeks for sJIA and 4 weeks for pJIA and adult RA. PK parameters presented for pJIA is from Part I of WA19977 (std1_pk_1). All PK parameters were PK model computed parameters except for MRA318JP where non-compartmental analysis was used for PK calculation.

Immunogenicity (Part I and II)

One patient (patient 2342) developed positive neutralizing anti-TCZ antibodies at Week 20. Available post dose PK concentrations from baseline through week 12 were comparable to those from other patients. Because this patient did not receive TCZ dosing at Week 8, she did not have model-computed PK exposure results from the study.

2.2.2.2. Pharmacodynamics

Following TCZ dosing, pronounced changes were observed in the inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The decline in median CRP concentrations and median ESR occurred rapidly, within the first two weeks of TCZ dosing. The observed changes in CRP and ESR were similar between the 10 mg/kg (<30 kg) and 8 mg/kg (≥30 kg) treatment groups, but were smaller in magnitude in the 8 mg/kg (<30 kg) group. The median CRP levels stabilized by week 8 for the 10 mg/kg (<30 kg) and 8 mg/kg (≥30 kg) groups but not until week 16 for the 8 mg/kg (<30 kg) group. The median ESR was lower in the 10 mg/kg (<30 kg) and 8 mg/kg (≥30 kg) treatment groups compared to the 8 mg/kg (<30 kg) group from week 2 through week 16.

2.2.2.3. Discussion on Clinical Pharmacology

Data on the PK and PD characteristics of TCZ have been previously submitted as part of the initial MAA and as part of variation II/15 to extend the indication of TCZ to the treatment of sJIA. This submission includes new data in pJIA patients.

Comparable exposure between the 10 mg/kg dose in the lower bodyweight patients (<30 kg) and the patients in the 8 mg/kg (≥30 kg) was observed, although a trend to somewhat lower exposure even in the higher dose for the lower bodyweight patients (<30 kg) was observed. Exposure in patients (<30 kg) dosed with 8 mg/kg was consistently lower compared to the other two dose groups. Of note, a different dosage was selected for the sJIA study. In this study it was demonstrated that doses of 8 and 12 mg/kg in the respective body weight groups lead to almost 100% bioequivalent exposure (shown for the two-weekly application). However, it is reassuring that the 8 and 10 mg/kg have demonstrated comparable efficacy in the respective patient groups.

Comparing the PK exposure to the JIA ACR30/50/70/90 response, a trend towards lower exposures in non-responders compared with responders, across JIA ACR30/50/70/90 was observed. This is even more pronounced for JIA ACR30 and JIA ACR50. Comparing the mean PK exposures across non-responders for JIA ACR30/50/70/90, there is a trend towards lower exposures in the least responsive patients (i.e. JIA ACR30 non-responders).

In contrast, when the mean pharmacokinetic exposures were compared across responders for JIA ACR30/50/70/90, there was no trend observed. The Applicant suggested that lower exposures are associated with complete non-response (failure to achieve JIA ACR30), whereas, in responders, variability in degree of response (between JIA ACR30 and 90) is explained by factors other than variability in PK exposure. However there is an overlap of patients in the responder groups. The relationship was based on cumulative AUC rather than single dose interval AUC. The MAH was requested during the evaluation to provide the percentage of ACR 30/50/70/90 response, the percentage of "ACR30 flare: no" reached and the percentage of dosage regimen applied (8 or 10 mg/kg) for each of the exposure quartile groups.

From the data provided by the MAH it seems there is no straight relationship between single-dose exposure data and responder rates. Paradoxically the responder rates of the lowest and highest Ctrough quartiles are similar and between them the responder rates are somewhat lower. Due to the small sample size it cannot be decided that the observed U type relationship is a chance finding or a real phenomenon. This statement is particularly true for the <30 kg weight group where are very few observations or sometimes even zero observations per cells.

Comparing the PK exposure to the safety profile no consistent trend of an increased risk of AEs with increased exposure was observed. A relationship between TCZ exposure and neutrophil loss was demonstrated in adult RA patients and in sJIA patients. Thus the higher incidence of infections in the highest exposure quartile (Q4) compared to the other quartiles is not unexpected.

Observed and model-computed PK parameters for the 10 mg/kg dose in patients weighing <30 kg to PK exposures, in both part I and part II, were more comparable to the 8 mg/kg dose in pJIA patients weighing ≥30 kg than for the 8 mg/kg (<30 kg) group. Especially comparable efficacy outcomes (JIA ACR response and JADAS27 change from baseline) for the 10 mg/kg dose in patients weighing < 30 kg and the 8 mg/kg dose in patients weighing ≥ 30 kg was demonstrated.

In contrast, no clear PK / safety relationship was observed. Thus the recommended dose of 10 mg/kg for pJIA patients weighing less than 30 kg and 8 mg for patients weighing ≥30 kg is acceptable.

2.2.2.4. Conclusions on Clinical Pharmacology

The MAH submitted with this extension of indication population PK analyses for studies WA19977 and MRA318JP.

The results for PK, PD, and exposure-response relationship from study WA19977 demonstrate that the lower exposure observed in patients who received the dose of 8 mg/kg in the low weight band was

associated with less marked change in PD markers and sub-optimal efficacy. Conversely, in the exposure range corresponding to the dose of 10 mg/kg in the lower weight band and to 8 mg/kg in the upper weigh band, the PD and efficacy were constant indicating a plateau of the TCZ exposure response curve was reached. In contrast to the evident PK-PD and PK-efficacy relationship, there was no clear exposure-safety relationship. These results demonstrate that optimal benefit can be achieved without an increased safety risk. Therefore, the dose of TCZ for the treatment of pJIA should be 10 mg/kg for patients weighing <30 kg and 8 mg/kg for patients weighing ≥30 kg is supported by the CHMP.

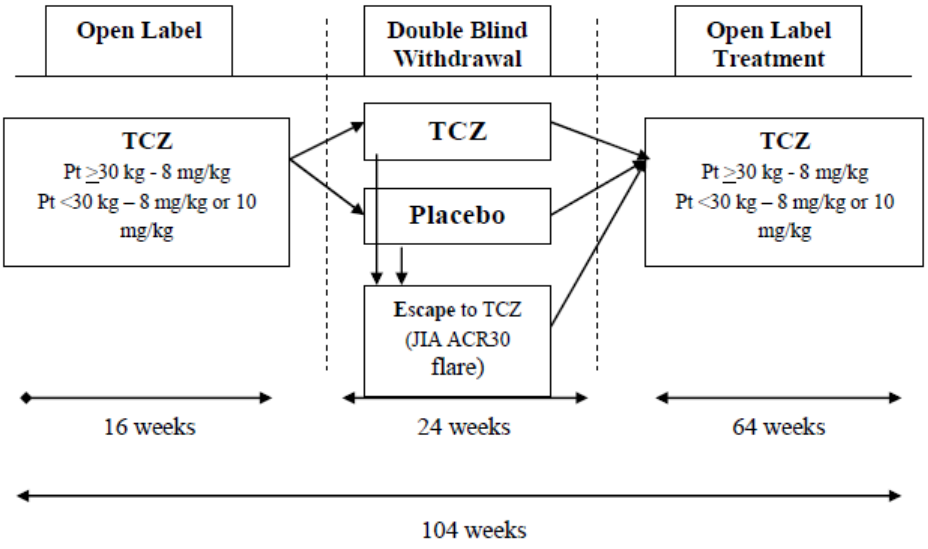
2.2.3. Clinical Efficacy

Study WA19977

Methods

Study WA19977was a 24-week randomized double-blind, placebo controlled withdrawal trial with a 16-week open-label lead-in phase, and 64-week open-label follow-up, to evaluate the efficacy and safety of tocilizumab in patients with active polyarticular juvenile idiopathic arthritis.

Figure 2. Overview of Study Design



Part I consisted of a 16-week active treatment lead in period, followed by Part II a randomized blinded withdrawal for a maximum of 24 weeks or occurrence of JIA ACR30 flare (compared to week 16). Beginning at week 16, patients with at least a JIA ACR30 response compared to baseline were randomized in a 1:1 ratio to enter the blinded withdrawal period (Part II) to either receive placebo or continue on active tocilizumab treatment at the same dose received in Part I.

No reductions or changes of concomitant NSAIDs, corticosteroids or methotrexate dosing were permitted during Part I and II, except for documented safety reasons.

Part III which is currently ongoing is a 64 week open-label period beginning at week 40 to examine the long term use of tocilizumab on safety and efficacy. In patients not receiving corticosteroids with inactive disease for at least 6 months, methotrexate tapering/discontinuation was considered if applicable.

Study participants

The target patient population of study WA19977 was patients of 2 to 17 years of age with documented evidence for at least 6 months prior to study entry of RF-positive or RF negative pJIA or of extended oligoarticular arthritis according to ILAR criteria. Disease had to be active at screening and baseline with at least five joints with active arthritis (joints that were swollen or if no swelling was present limitation of movement accompanied by pain, tenderness or both), with at least 3 of the active joints having limitation of motion. The patients also had to have had an inadequate response to methotrexate (MTX) or inability to tolerate MTX. Patients previously treated with any cell depleting therapy, including any investigational agents (e.g. anti-CD19 and anti-CD20) were not permitted in the study.

The following JIA subtypes were not included in the study population: systemic arthritis, persistent oligoarthritis, psoriatic arthritis, enthesitis related arthritis, and undifferentiated arthritis.

Treatments

Part I: Active treatment lead-in period, every 4 weeks for 4 doses. The total duration was 16 weeks with dosing at baseline, Weeks 4, 8 and 12.

- <30 kg randomized 1:1 to either TCZ 8 mg/kg or 10 mg/kg intravenous (IV) infusion
- ≥30 kg TCZ 8 mg/kg IV infusion

Part II: Double-blind withdrawal period. All subjects were randomized to either:

- TCZ (at the same dose as Part I)
- Placebo

This withdrawal period lasted from Week 16 through Week 40 with the last dose at Week 36.

Part III: Open-Label (Part I dose resumed)

Concurrent use of DMARDs and immunosuppressants other than methotrexate was not permitted in the study. Oral corticosteroids were allowed concomitantly during the study.

In Part III of the study concomitant medications were allowed to be reduced for efficacy only according in the following order: oral corticosteroids first, methotrexate second and NSAIDs last.

Objectives

Primary Objective (from Part II)

The primary objective of the study was to compare the proportion of patients on tocilizumab (TCZ) versus placebo who developed a juvenile idiopathic arthritis (JIA) American College of Rheumatology 30 (ACR30) flare (compared to Week 16) by Week 40.

Secondary Objectives

- To evaluate the efficacy of open-label TCZ therapy (Part I)
- To evaluate the long-term effect of TCZ on the maintenance of clinical response and safety in patients with polyarticular JIA (pJIA) (Parts II and III)
- To evaluate the efficacy and safety of 8 mg/kg vs. 10 mg/kg in patients <30 kg (Parts I, II and III)

Outcomes/endpoints

Part I (not exhaustive)

- JIA ACR Core set

Clinical measures of efficacy were evaluated by comparing the following JIA ACR core outcome variables to baseline values. JIA ACR responses were defined as follows:

  - JIA ACR30 response was 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%
  - JIA ACR50/70/90 responses were defined in a similar manner for 50%, 70% and 90% improvements.

- JADAS-27

Juvenile Arthritis Disease Activity Score (JADAS-27), a composite disease: derived from 6 variables including:

- Parent/patient global assessment of overall wellbeing
- Physician global assessment of disease activity
- Normalised ESR
- Arthritis activity at 27 selected joints Number of joints with limitation of movement
- ESR
- Functional Ability determined by CHAQ Disability Index.

The patient were deemed to have responded if 3 of the 6 core variables have improved by at least 30% at week 16 and not more than one of the other core variables has worsened by 30% or more.

Part II

JIA ACR30 flare was defined for Part II of the study as a change from Week 16 of:

- At least 3 of the 6 JIA ACR components worsening by at least 30% and
- No more than 1 of the remaining JIA ACR components improving by no more than 30%.

Additional criteria addressing worsening in patients with a very low Week 16 score (ie, 30% improvement had to be substantive) were also specified.

Table 6. Hierarchical fixed sequence of efficacy endpoints

Order No.	Primary Endpoint
1	Proportion of patients who develop a JIA ACR30 flare (relative to Week 16) in the period from Week 16 up to and including Week 40
	Secondary Endpoint
2	Proportion of patients with a JIA ACR30 response (relative to baseline) at Week 40
3	Proportion of patients with a JIA ACR50 response (relative to baseline) at Week 40
4	Proportion of patients with a JIA ACR70 response (relative to baseline) at Week 40
5	Change from baseline in number of joints with active arthritis at Week 40
6	Change from baseline in physician's global assessment of disease activity VAS at Week 40
7	Change from baseline in pain VAS at Week 40
8	Change from baseline in number of joints with limitation of movement at Week 40
9	Change from baseline in parent/patient's global assessment of overall well-being VAS at Week 40
10	Change from baseline in ESR at Week 40
11	Change from baseline in CHAQ-DI score at Week 40
12	Proportion of patients with a JIA ACR90 response (relative to baseline) at Week 40
13	Proportion of patients with inactive disease at Week 40

VAS: visual analogue scale.

Sample size

Assuming a 35% flare rate in the TCZ arm and a 65% flare rate in the placebo arm, 60 patients with polyarticular-course JIA were to be randomized per arm in Part II to achieve at least 80% power to detect this difference applying a Type I error of 0.05 (2-sided). In order to achieve these numbers 185 patients were to be recruited into Part I of the study.

Randomisation

Randomization in part II to TCZ or placebo in a 1:1 ratio was stratified by concurrent methotrexate use and concurrent corticosteroid use.

Blinding

Part II of the study was a 24-week double-blind withdrawal period. Patients entering the withdrawal period of the study (Part II) were randomized equally to receive either TCZ or placebo, stratified by methotrexate and oral corticosteroid use.

To preserve the blind, various vial combinations based on the patient's weight with identical appearance for both treatments were used. To prevent potential blind breaks due to observed efficacy or laboratory changes a 'dual assessor' approach was used to evaluate efficacy and safety during Part I and Part II of the study. The joint assessor performing all joint examinations in Part I and Part II was blinded. CRP results after the first dose of study drug remained blinded to all study participants in order to preserve the blind during Part II.

Statistical methods

For study parts I and II all efficacy parameters were summarized by statistical characteristics, depending of the type of data, stratified by treatment and visit (if appropriate).

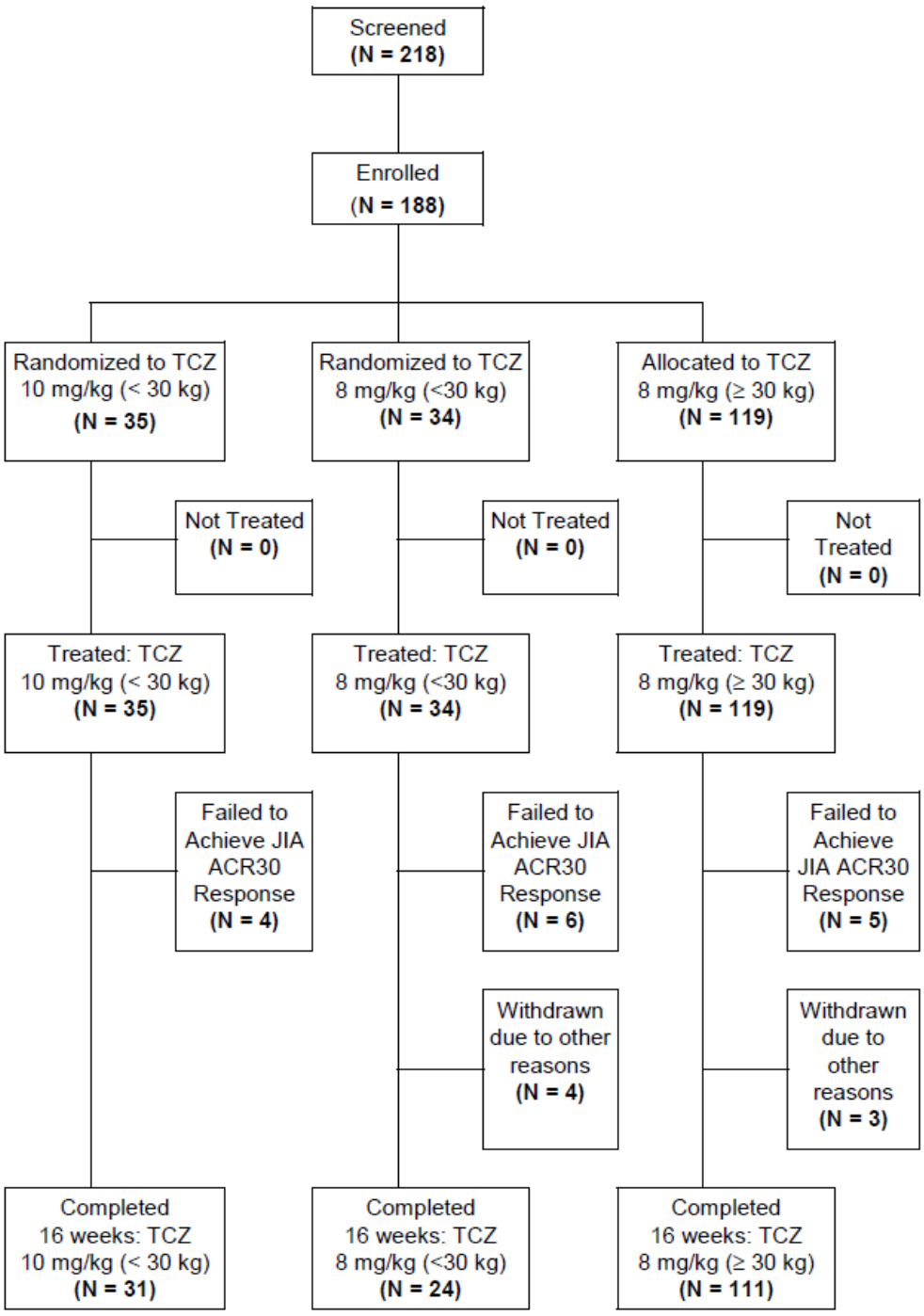
The main efficacy analysis population was the ITT population in Part II (ITT-2) consisting of all patients who were randomized into Part II and received at least one dose of study drug.

For Part II a Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification factors used for randomisation was used to compare the rate of JIA ACR30 flares between TCZ and placebo. Secondary parameters were analysed by means of CMH-tests (in case of dichotomous outcomes) or ANOVA-models (continuous data). To control the Type I error a pre-defined hierarchical fixed sequence approach was applied. Each endpoint in the sequence had to be significant ($p<0.05$) in order for the subsequent endpoint in the chain to be tested. To account for missing data the following approach was used: for categorical endpoints, patients with missing data were classified as 'non-responders'. For continuous data the 'observed data' approach was used for Part I and LOCF imputation was used for Part II.

Results

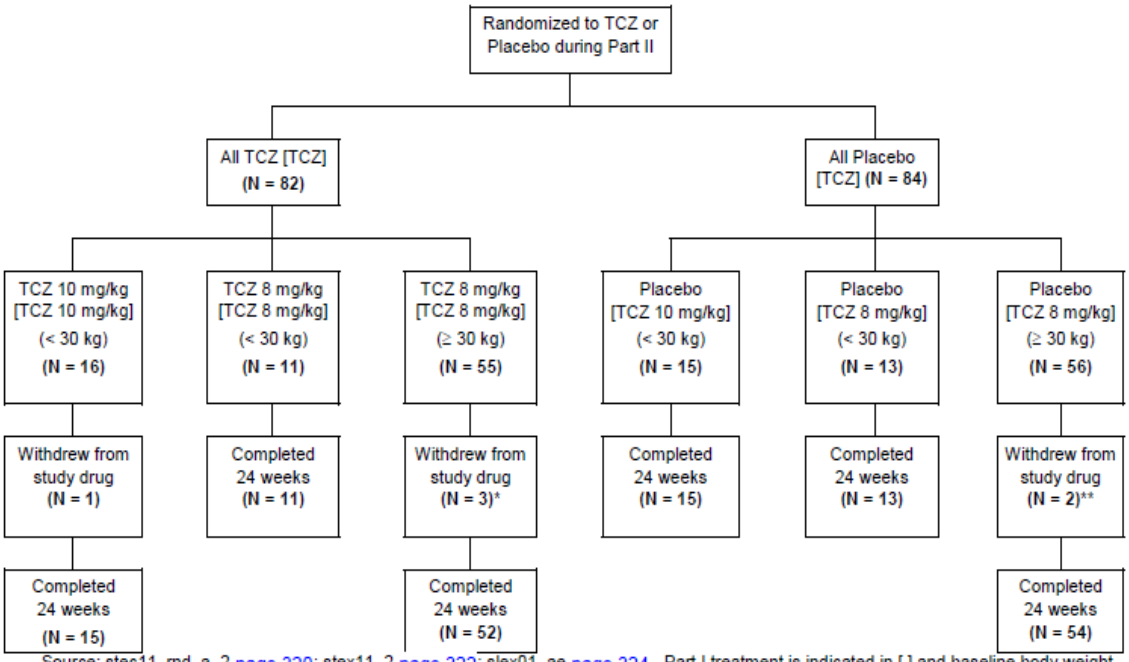
Participants flow

Figure 3. Patient Disposition (Part I)



Twenty two patients withdrew in Part I the majority of which were due to lack of therapeutic effect (15 patients) and were not permitted to continue to Part II. Other withdrawals during Part I were due to AEs (3 patients), refusal of treatment (3 patients) and lost to follow-up (1 patient).

Figure 4. Patient Disposition (Part II)



Source: stec11_md_a_2 page 320; stex11_2 page 322; slex01_ae page 324. Part I treatment is indicated in [ ] and baseline body weight category in ( ).

* Patient 2583 did not receive a randomized dose and was excluded from Part II (the patient missed the Week 16 infusion, completed Week 18 and then withdrew at the next visit). Patients 2122 and 2682 withdrew while receiving Part II escape medication and were therefore excluded from the Part II withdrawal summary.

** Patient 2133 was a Part I withdrawal but was randomized in error and was excluded from the Part II population.

Recruitment

The study was conducted from 14 October 2009 until 4 November 2011.

Conduct of the study

85 sites for this study enrolled subjects in Argentina, Australia, Belgium, Brazil, Canada, France, Germany, Italy, Mexico, Peru, Poland, Russia, Spain, the UK and the USA.

The study protocol was amended twice. There were no changes to the planned analyses as originally specified in the SAP that significantly affected or altered the analysis of efficacy and safety data.

Baseline data

Table 7. Demographic and disease characteristics

	TCZ 10 mg/kg (< 30 kg) (N = 35)	TCZ 8 mg/kg (< 30 kg) (N = 34)	TCZ 8 mg/kg (≥ 30 kg) (N = 119)	All TCZ (N = 188)
Age (years), mean (SD)	6.9 (3.02)	7.6 (2.71)	13.1 (2.78)	11.0 (4.01)
Females, n (%)	30 (86)	24 (71)	90 (76)	144 (77)
White Race, n (%)	28 (80)	28 (82)	94 (79)	150 (80)
Non-Hispanic Ethnicity, n (%)	22 (63)	23 (68)	80 (67)	125 (66)
Weight (kg), mean (SD)	20.7 (5.7)	22.4 (5.3)	50.0 (12.6)	39.6 (17.3)
Height (cm), mean (SD)	117.1 (15.3)	120.4 (14.1)	153.7 (13.7)	140.8 (22.0)
Body surface area (m^2), mean (SD)	0.8 (0.17)	0.9 (0.16)	1.5 (0.22)	1.2 (0.36)
Disease duration (years), mean (SD)	3.4 (2.39)	3.5 (2.57)	4.7 (4.16)	4.2 (3.67)
Prior DMARDs use, n (%)	21 (60)	26 (76)	87 (73)	134 (71)
Prior biologics use, n (%)	8 (23)	6 (18)	47 (39)	61 (32)
Number of Joints with Active Arthritis, mean (SD)	23.9 (18.3)	21.2 (13.6)	18.9 (13.0)	20.3 (14.3)
Number of Joints with LOM, mean (SD)	23.1 (19.2)	17.3 (13.3)	16.0 (12.7)	17.6 (14.4)
Patient/Parent Global Assessment VAS, mean (SD)	51.5 (26.9)	59.1 (26.2)	51.6 (24.1)	52.9 (25.0)
Physician Global Assessment VAS, mean (SD)	64.7 (20.5)	64.7 (18.5)	59.4 (21.3)	61.4 (20.7)
CHAQ-DI Score, mean (SD)	1.7 (0.71)	1.8 (0.68)	1.2 (0.69)	1.4 (0.74)
ESR, mean (SD)	35.1 (24.1)	36.6 (23.0)	34.2 (26.7)	34.8 (25.5)
Concurrent Methotrexate Use, n (%)	29 (83)	30 (88)	89 (75)	148 (79)
Median Dose mg/m^2/week	14.3	14.1	11.4	11.8
Corticosteroid Use, n (%)	15 (43)	18 (53)	54 (45)	87 (46)
Average Dose (mg/kg/day) (SD)	0.15 (0.033)	0.15 (0.038)	0.12 (0.052)	0.13 (0.048)

The majority of patients were RF-negative (126 [67%]) at baseline compared to 54 (29%) patients who were RF-positive; 8 (4%) patients had missing RF status at baseline.

Numbers analysed

All 188 patients enrolled received at least 1 infusion of TCZ and were therefore included in the ITT population, which was used in the analyses of efficacy data.

Outcomes and estimations

Primary endpoint

The primary efficacy endpoint of the study was difference in JIA ACR30 flare rate between Week 16 and Week 40 in patients receiving placebo and those receiving TCZ.

Table 8. Cochran-Mantel-Haenszel Analysis of the Proportion of Patients with JIA ACR30 Flare (Withdrawal Phase Study Part II, ITT Population – Study Part II)

	ALL PLACEBO [TCZ] (N=81)	ALL TCZ [TCZ] (N=82)
n	81	82
Flared	39 (48.1%)	21 (25.6%)
95% C.I.	[0.37; 0.59]	[0.16; 0.35]
Weighted difference vs. ALL PLACEBO [TCZ]		-0.21
95% C.I. of weighted difference		[-0.35;-0.08]
p-value		0.0024

Flared are patients who developed a JIA ACR30 flare (relative to Week 16) in the period from Week 16 up to and including Week 40.
Patients who withdrew or who took escape medication are classified as flared.
Analysis adjusted for the randomization stratification factors (background use of methotrexate and background use of oral corticosteroids) applied at Week 16.
Treatment comparison is vs. All Placebo [TCZ].
C.I. = Confidence Interval.
For treatment groups the treatment received in the study part I lead-in phase is indicated in [ ].

There was also a statistically significant treatment difference (p-value 0.0003) in the robustness analysis of JIA ACR30 flare (withdrawn patients assigned as not flared). The 12 patients who were randomized at Week 16 but withdrew or took escape medication prior to Week 40 without experiencing a JIA ACR30 flare were not influential in determining the treatment effect.

Secondary endpoints

To control for the Type I error rate the secondary endpoints were tested in a hierarchical fixed sequence approach. Each endpoint in the sequence had to be significant ($p<0.05$) in order for the subsequent endpoint in the chain to be considered significant.

Table 9. Overview of Hierarchical Analysis of Significance Testing at Week 40

	Endpoint	All Placebo N=81	All TCZ N=82	p-value
Primary Endpoint				
1	Proportion with JIA ACR30 flare (relative to Week 16)	39 (48.1%)	21 (25.6%)	0.0024
Secondary Endpoints				
2	Proportion of patients with JIA ACR30 Improvement Number (%)	44 (54.3%)	61 (74.4%)	0.0084
3	Proportion of patients with JIA ACR50 Improvement Number (%)	42 (51.9%)	60 (73.2%)	0.0050
4	Proportion of patients with JIA ACR70 Improvement Number (%)	34 (42.0%)	53 (64.6%)	0.0032
5	Change from baseline in number of active joints Adjusted Mean	−11.4	−14.3	0.0435
6	Change from baseline in Physician's global assessments VAS Adjusted Mean	−35.2	−45.2	0.0031
7	Change from Baseline in the Pain VAS Adjusted Mean	−22.3	−32.4	0.0076
8	Change from baseline in number of joints with limitation of movement, Adjusted Mean	−7.7	−9.5	0.1229
9	Patient/parent global assessment VAS Adjusted Mean	−24.7	−32.1	******
10	Change from baseline in ESR (mm/hr) Adjusted Mean	−12.0	−26.3	******
11	CHAQ-DI score	−0.6	−0.8	******
12	Proportion with JIA ACR90 improvement Number (%)	19 (23.5%)	37 (45.1%)	******
13	Proportion with Inactive Disease Number (%)	12 (14.8%)	26 (31.7%)	******

****** p-values for these variables are not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity

The hierarchical chain of assessment for secondary endpoints for the study was broken at the assessment of number of joints with limitation of movement and hence treatment significance was not assessed below that point in the chain of assessments.

Part I

Table 10. Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16 (ITT Population - Part I)

	TCZ 10 MG/KG (<30KG) (N=35)	TCZ 8 MG/KG (<30KG) (N=34)	TCZ 8 MG/KG (>=30KG) (N=119)	ALL TCZ (N=188)
Week 16				
n	35	34	119	188
JIA ACR30 Response	31 (88.6%)	26 (76.5%)	111 (93.3%)	168 (89.4%)
JIA ACR50 Response	28 (80.0%)	24 (70.6%)	104 (87.4%)	156 (83.0%)
JIA ACR70 Response	22 (62.9%)	14 (41.2%)	81 (68.1%)	117 (62.2%)
JIA ACR90 Response	11 (31.4%)	8 (23.5%)	30 (25.2%)	49 (26.1%)

Responders are patients who had a JIA ACR30/50/70/90 response (relative to Baseline) at the visit.
Patients who withdrew or for whom the endpoint could not be determined are classified as non-responders.
For treatment groups the body weight category at Baseline is indicated in ().

Table 11. JADAS-27 Score (0-57) and Mean Change From Baseline at Week 16 (Lead-in Phase Study Part I , ITT Population – Study Part I)

	TCZ 10 MG/KG (<30KG) (N=35)	TCZ 8 MG/KG (<30KG) (N=34)	TCZ 8 MG/KG (>=30KG) (N=119)	ALL TCZ (N=188)
Baseline				
n	35	34	118	187
Mean	28.20	27.53	25.05	26.09
SE	2.145	1.584	0.845	0.729
SD	12.688	9.234	9.177	9.972
Median	27.88	26.73	24.38	25.10
Min-Max	9.1-50.1	9.5-46.3	9.3-51.3	9.1-51.3
Week 16				
n	35	31	116	182
Mean	9.08	12.25	7.83	8.82
SE	1.501	1.846	0.661	0.608
SD	8.882	10.277	7.122	8.198
Median	5.10	10.10	6.30	6.30
Min-Max	0.0-33.0	0.0-36.7	0.0-30.5	0.0-36.7
Week 16 Change from Baseline				
n	35	31	115	181
Mean	-19.12	-15.17	-17.17	-17.21
SE	2.295	1.544	0.685	0.676
SD	13.578	8.595	7.350	9.099
Median	-13.54	-13.58	-17.50	-16.90
Min-Max	-42.4-6.9	-34.9--1.5	-33.9-2.2	-42.4-6.9

A negative change indicates improvement.
Each visit includes patients with a non-missing assessment at the timepoint. Patients who previously withdrew are excluded.
JADAS-27 (0 - 57) calculated from the physician's global assessment of disease activity and parent/patient's global assessment of overall well-being VAS (0 - 10 cm), number of selected joints with active arthritis (0 - 27) and normalized ESR (0 - 10).
JADAS = Juvenile Arthritis Disease Activity Score.
SD = Standard Deviation. SE = Standard Error of the mean.
For treatment groups the body weight category at Baseline is indicated in ().

Program : $PROD/cs11935j/j19977a/etefsum01.sas
Output : $PROD/cs11935j/j19977a/reports/
02FEB2012 17:17 Page 1 of 1
Sources:etefsum01_j27r_v2b_rtf_p1.out, and etefsum01_cj27r_v2_rtf_p1.out

Seventy-eight patients had an elevated CRP concentration (>10 mg/L) at baseline. The concentration had normalized 2 weeks after their first dose of TCZ in the majority of these patients (76/78 [97.4%]). The proportion with a normalized CRP increased to Week 16. The proportion of patients with normalized CRP at 16 weeks was lower for the lighter children (<30 kg) who were receiving the lower dose (8 mg/kg) of TCZ than the heavier children (>30 kg) or than those receiving the higher dose (10 mg/kg) of TCZ.

From Week 16 to Week 40, patients randomized to TCZ maintained their Week 16 response. Patients randomized to placebo experienced a dramatic increase in mean ESR as soon as they stopped receiving TCZ.

Ancillary analyses

Gender: There were no differences in the JIA ACR 30/50/70/90 response rate profile of subgroups.

Age: A smaller proportion of patients aged ≤7 years achieved JIA ACR 30/50/70 responses than patients aged ≥8 years.

Table 12. Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16, by Age at Baseline (Lead-in Phase Study Part I , ITT Population - Study Part I)

	TCZ 10 MG/KG (<30KG)	TCZ 8 MG/KG (<30KG)	TCZ 8 MG/KG (>=30KG)	ALL TCZ
Age at Baseline: <= 7 years				
Week 16				
n	19	17	2	38
JIA ACR30 Response	17 (89.5%)	11 (64.7%)	2 (100.0%)	30 (78.9%)
JIA ACR50 Response	16 (84.2%)	10 (58.8%)	2 (100.0%)	28 (73.7%)
JIA ACR70 Response	14 (73.7%)	7 (41.2%)	1 (50.0%)	22 (57.9%)
JIA ACR90 Response	5 (26.3%)	5 (29.4%)	0 (0.0%)	10 (26.3%)
Age at Baseline: 8-12 years				
Week 16				
n	16	16	50	82
JIA ACR30 Response	14 (87.5%)	15 (93.8%)	49 (98.0%)	78 (95.1%)
JIA ACR50 Response	12 (75.0%)	14 (87.5%)	46 (92.0%)	72 (87.8%)
JIA ACR70 Response	8 (50.0%)	7 (43.8%)	33 (66.0%)	48 (58.5%)
JIA ACR90 Response	6 (37.5%)	3 (18.8%)	12 (24.0%)	21 (25.6%)
Age at Baseline: >= 13 years				
Week 16				
n	0	1	67	68
JIA ACR30 Response	0 (0.0%)	0 (0.0%)	60 (89.6%)	60 (88.2%)
JIA ACR50 Response	0 (0.0%)	0 (0.0%)	56 (83.6%)	56 (82.4%)
JIA ACR70 Response	0 (0.0%)	0 (0.0%)	47 (70.1%)	47 (69.1%)
JIA ACR90 Response	0 (0.0%)	0 (0.0%)	18 (26.9%)	18 (26.5%)

Responders are patients who had a JIA ACR30/50/70/90 response (relative to Baseline) at the visit.
Patients who withdrew or for whom the endpoint could not be determined are classified as non-responders.
For treatment groups the body weight category at Baseline is indicated in ( ).

Program : $PROD/cs11935j/j19977a/etepfrq01.sas / Output :
$PROD/cs11935j/j19977a/reports/etepfrq01_w16_bage_it1_ap1.out
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Duration of disease: A smaller proportion of patients with longer duration of disease achieved JIA ACR 30/50/70/90 improvement than patients with disease duration of ≤2 years.

Table 13. Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16, by Rheumatoid Factor at Baseline (Lead-in Phase Study Part I, ITT Population - Study Part I)

	TCZ 10 MG/KG (<30KG)	TCZ 8 MG/KG (<30KG)	TCZ 8 MG/KG (>=30KG)	ALL TCZ
RF: Positive				
Week 16				
n	4	2	48	54
JIA ACR30 Response	3 (75.0%)	2 (100.0%)	43 (89.6%)	48 (88.9%)
JIA ACR50 Response	3 (75.0%)	2 (100.0%)	43 (89.6%)	48 (88.9%)
JIA ACR70 Response	3 (75.0%)	2 (100.0%)	38 (79.2%)	43 (79.6%)
JIA ACR90 Response	2 (50.0%)	0 (0.0%)	15 (31.3%)	17 (31.5%)
RF: Negative				
Week 16				
n	31	30	65	126
JIA ACR30 Response	28 (90.3%)	22 (73.3%)	62 (95.4%)	112 (88.9%)
JIA ACR50 Response	25 (80.6%)	21 (70.0%)	55 (84.6%)	101 (80.2%)
JIA ACR70 Response	19 (61.3%)	12 (40.0%)	38 (58.5%)	69 (54.8%)
JIA ACR90 Response	9 (29.0%)	8 (26.7%)	13 (20.0%)	30 (23.8%)
RF: Missing				
Week 16				
n	0	2	6	8
JIA ACR30 Response	0 (0.0%)	2 (100.0%)	6 (100.0%)	8 (100.0%)
JIA ACR50 Response	0 (0.0%)	1 (50.0%)	6 (100.0%)	7 (87.5%)
JIA ACR70 Response	0 (0.0%)	0 (0.0%)	5 (83.3%)	5 (62.5%)
JIA ACR90 Response	0 (0.0%)	0 (0.0%)	2 (33.3%)	2 (25.0%)

Responders are patients who had a JIA ACR30/50/70/90 response (relative to Baseline) at the visit.
Patients who withdrew or for whom the endpoint could not be determined are classified as non-responders.
For treatment groups the body weight category at Baseline is indicated in ( ).

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MTX use: At baseline 79% of patients were taking concurrent MTX. From Week 16 to 40, a lower proportion of patients experienced JIA ACR30 flares in the subgroup who were taking concurrent MTX (Table 20). However, regardless of MTX use, the incidence of JIA ACR30 flare was lower for patients receiving TCZ to those receiving placebo.

Table 14. Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Background MTX Use at Baseline (Lead-in Phase Study Part I + Withdrawal Phase Study Part II, ITT Population Study Part II)

	All Placebo		All TCZ	
MTX Use	**Yes**	**No**	**Yes**	**No**
JIA ACR30 Flare	25 (39.1%)	14 (82.4%)	13 (19.4%)	8 (53.3%)
JIA ACR30 Response	39 (60.9)	5 (29.4)	53 (79.1)	8 (53.3)
JIA ACR50 Response	38 (59.4)	4 (23.5)	52 (77.6)	8 (53.3)
JIA ACR70 Response	30 (46.9)	4 (23.5)	45 (67.2)	8 (53.3)
JIA ACR90 Response	18 (28.1)	1 (5.9)	32 (47.8)	5 (33.3)

Source: etepfrq05_w40_bmtx_rx3_it2_ap12

Oral corticosteroid use: Oral corticosteroid use at baseline was also a stratification factor in the randomization of patients at Week 16. There was no consistent trend in the JIA ACR30 flare rate at Week 40 based on concurrent corticosteroid use.

Previous Biologic Use: The number of patients who received previous biologics was 32% with the remaining 68% being biologic-naïve.

JIA ACR30 flare rate was higher and JIA ACR responses were lower at Week 40 in patients that had previously been exposed to a biologic (TCZ and placebo groups) compared to biologic-naïve patients (Table 21). However, patients randomized to TCZ responded better than patients receiving placebo whether they had prior biologic use or not.

Table 15. Proportion of Patients with a JIA ACR30 Flare and Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Previous Biologic Use (Lead-in Phase Study Part I + Withdrawal Phase Study Part II, ITT Population – Study Part II)

	All Placebo		All TCZ	
Biologic Use	**Yes (N = 23)**	**No (N = 58)**	**Yes (N = 27)**	**No (N = 55)**
JIA ACR30 Flare	18 (78.3)	21 (36.2)	12 (44.4)	9 (16.4)
JIA ACR30 Response	6 (26.1)	38 (65.5)	15 (55.6)	46 (83.6)
JIA ACR50 Response	5 (21.7)	37 (63.8)	14 (51.9)	46 (83.6)
JIA ACR70 Response	2 (8.7)	32 (55.2)	13 (48.1)	40 (72.7)
JIA ACR90 Response	2 (8.7)	17 (29.3)	5 (18.5)	32 (58.2)

Source: etepfrq05_w40_bbio_rx3_it2_ap12 page 691

Supportive Studies

Study MRA318JP

This study was a phase III open-label study of TCZ in patients with juvenile idiopathic arthritis involving multiple active joints. 5 sites enrolled subjects in Japan. Patients who met all the criteria below were included as subjects of this study:

1. Patients diagnosed as having RF-positive or RF-negative polyarticular JIA or oligoarticular JIA using the ILAR criteria (1997)

2. Patients between 2 and 19 years of age
3. Patients who were under 16 years of age at onset
4. Patients who met all the following criteria at enrolment (within 2 weeks before the start of treatment with the investigational product)
5. Pain/tenderness and limited range of motion in 3 or more of the 74 joints examined
6. Inflammatory swelling in 5 or more of the 74 joints examined
7. ESR (Westergren method) ≥30 mm/hr or CRP ≥1.0 mg/dL
8. Patients for whom written informed consent for participation in the study had beenobtained from the parents (or legal guardian). (Written informed consent was also obtained from the patient personally if the patient had the necessary level of understanding.)

TCZ was intravenously infused at a dose of 8 mg/kg three times at 4-week intervals.

Primary endpoint

Percentage of patients showing 30% improvement in the JIA core set on the last observation day.

Secondary endpoints

- Time courses of percentage of patients showing 30%, 50% and 70% improvement in the JIA core set up to the last observation day
- Time courses of the JIA core set components up to the last observation day
- Time course of CRP up to the last observation day
- Time course of pain up to the last observation day

The serum TCZ concentration and pharmacokinetic parameters (e.g., C_{max}, time course of trough value, AUC, k_{el}, CL, V_d, V_{dss}, $t_{1/2}$) were evaluated. Patients who received one or more doses of the investigational product formed the analysis set for the pharmacokinetic analysis. The patients were handled as shown in the figure below. The patients were classified according to the following criteria. In this clinical study, the PPS (population complying with protocol) formed the main analysis set for efficacy.

Results

Nineteen patients were enrolled in the study. In all 19 patients, the investigational product was administered three times as specified and the last observations were completed. None of the patients was withdrawn.

The patients were made up of 4 males and 15 females. Their age (mean ± SD [range]; same hereinafter) was 11.6 ± 5.3 (3 to 19) years, age at onset of the underlying disease was 6.2 ± 4.0 (0 to 14) years and the disease duration was 5.3 ± 4.5 (1 to 17) years. At baseline, CRP was 2.657 ± 1.985 (0.06 to 8.2) mg/dL, ESR was 46.5 ± 19.9 (18 to 83) mm/hr, the number of joints with active arthritis was 14.3 ± 9.5 (5 to 43) and the number of joints with limited range of motion was 9.4 ± 6.8 (1 to 21). Fifteen patients were being treated with corticosteroids at the start of treatment. The prednisolone-equivalent dose (the daily dose on the day treatment was started) was 0.141 ± 0.071 (0.02 to 0.30) mg/kg and 4.73 ± 2.98 (1.0 to 10.0) mg/body.

Time courses of the percentage of patients showing 30%, 50% and 70% improvement in the JIA core set up to the last observation day

The time courses of the percentage of patients showing 30%, 50%, 70% improvement in the JIA core set are shown in the figure and table below.

The JIA core set variables improved rapidly as a result of treatment with TCZ. The 0% improvement rate on the last observation day (primary endpoint) was 94.7% (18 of 19 patients), which was high. The 50% and 70% improvement rates were 94.7% (18 of 19 patients) and 57.9% (11 of 19 patients), respectively.

Figure 5. Time course of percentage of patients showing 30%, 50 % and 70 % improvement in the JIA core set

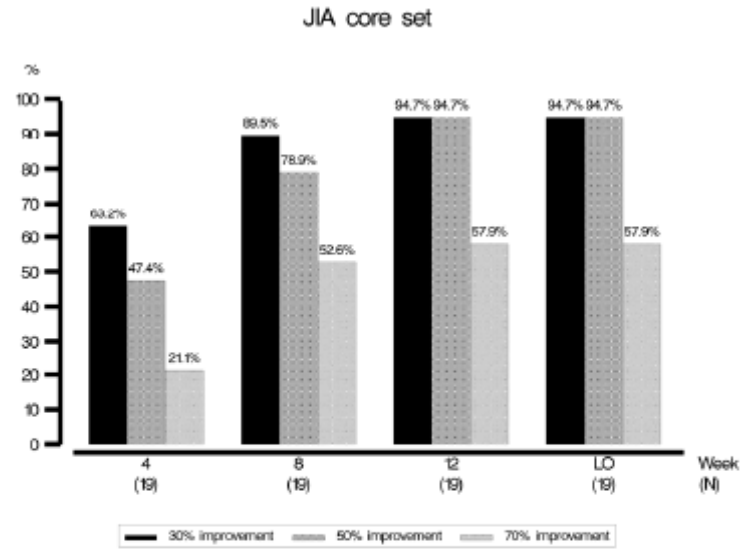


Table 16. Time courses of Percentage of Patients Showing 30%, 50 % and 70 % Improvement in the JIA Core Set

Summary of JIA Response Rates
Population : FAS

	Visit (Week)	N	Improved	Not improved	Improvement rate (%)	95%CI Lower - Upper
30% improvement						
	4	19	12	7	63.2	38.4 - 83.7
	8	19	17	2	89.5	66.9 - 98.7
	12	19	18	1	94.7	74.0 - 99.9
	LastOBS	19	18	1	94.7	74.0 - 99.9
50% improvement						
	4	19	9	10	47.4	24.4 - 71.1
	8	19	15	4	78.9	54.4 - 93.9
	12	19	18	1	94.7	74.0 - 99.9
	LastOBS	19	18	1	94.7	74.0 - 99.9
70% improvement						
	4	19	4	15	21.1	6.1 - 45.6
	8	19	10	9	52.6	28.9 - 75.6
	12	19	11	8	57.9	33.5 - 79.7
	LastOBS	19	11	8	57.9	33.5 - 79.7

N represents number of patients contributing to summary statistics.
Percentages are based on N.
LastOBS:Last Observation

Study MRA319JP

This study was a phase IV study to investigate the safety, efficacy and pharmacokinetics of long-term treatment with TCZ in the 19 patients examined in the Open-label Clinical Study of TCZ in Patients with Polyarticular Juvenile Idiopathic Arthritis (hereinafter, “the previous study”), who were administered 8 mg/kg TCZ, as a rule, by intravenous infusion at 4- week intervals. 5 sites enrolled subjects in Japan. Patients who met all the criteria below were included as subjects in this study:

- Of the patients who received three infusions of TCZ in the previous study and for whom a last observation was conducted, those who did not have problems with safety and whose CRP or ESR level had improved with administration of TCZ
- Patients who wished to be treated with TCZ and whose parent/legal guardian gave written consent for participation in the study (written consent was also obtained from the patient if the patient had the capacity to understand.)

Dosage and administration: TCZ at a dose of 8 mg/kg, as a rule, at 4-week intervals by intravenous infusion. The dose and interval between infusions could be adjusted depending on changes in clinical signs and laboratory test values. However, the upper limit for one infusion was to be 8 mg/kg, and the shortest interval between infusions was to be two weeks (14 days). Duration of treatment: A target of at least one year from the first infusion in the previous study.

Primary endpoint:

The primary endpoint was the percentage of patients showing 30% improvement in the JIA core set compared with the baseline value of the previous study.

Secondary endpoints:

- Time courses of the percentages of patients showing 30%, 50% and 70% improvement in the JIA core set from the baseline value of the previous study
- The time course of each variable of the JIA core set from the baseline value of the previous study
- The time course of CRP from the baseline value of the previous study
- The time course of pain from the baseline value of the previous study.

The patients were handled as in the figure below. Patient classification was determined in accordance with the following criteria. Patient classifications were decided before data locking. In this study, the full analysis set (FAS) was the primary analysis set for efficacy.

Results

Nineteen patients were enrolled in the present study: 15 of them completed the study, and the other four were withdrawn. The 19 patients in the previous study were all enrolled in the present study. Four patients (21.1%) were withdrawn from the study. The reason for withdrawal was “absence of change in or aggravation of symptoms” for two patients (10.5%, Patient Nos. 05 and 18), “adverse event occurrence” for one patient (Patient No. 15) and “confirmation of appearance of anti-TCZ antibodies” for one patient (Patient No. 13). The continuation rate was high—94.7% (18 of 19 patients) after one year, 84.2% (16 of 19 patients) after two years and 78.9% (15 of 19 patients) after three years.

There were four male patients and 15 female patients. The age of the patients was 11.6 years ± 5.3 years (3–19 years) [mean ± SD (range), same below]; the age of the patients at onset of the underlying disease was 6.2 years ± 4.0 years (0–14 years); and the duration of the disease was 5.28 years ± 4.46 years (0.8–17.1 years). Baseline test values were as follows: CRP, 2.66 mg/dL ± 1.99 mg/dL (0.1–8.2 mg/dL); ESR, 46.5 mm/h ± 19.9 mm/h (18–83 mm/h); number of active joints, 14.3 joints ± 9.5 joints (5–43 joints); and number of joints with limited range of motion, 9.4 joints ± 6.8 joints (1–21 joints). In addition, 15 patients were being treated with corticosteroids at the start of treatment with TCZ, and the prednisolone-equivalent dose (daily dose on the first day of TCZ treatment) was 0.11 mg/kg ± 0.09 mg/kg (0.0–0.3 mg/kg) and 3.74 mg/body ± 3.29 mg/body (0.0–10.0 mg/body).

Outcomes and estimations

The percentages of patients showing 30%, 50% and 70% improvement in the JIA core set every 24 weeks compared with the respective values before the start of treatment in the present study are shown in the table below. The percentage of patients showing 30% improvement (the primary endpoint) was 94.1% (16 of 17 patients) after 24 weeks and 100.0% after each 24-week period from 48 weeks to 168 weeks (17 of 17 patients, 16 of 16 patients, 14 of 14 patients and 15 of 15 patients). The percentage of patients showing 50% improvement was 94.1% (16 of 17 patients) after both 24 weeks and 48 weeks, 100.0% after each 24-week period from 72 weeks to 144 weeks (16 of 16 patients and 14 of 14 patients), and 93.3% (14 of 15 patients) after 168 weeks. The percentage of patients showing 70% improvement was 94.1% (16 of 17 patients) after 24 weeks, 88.2% (15 of 17 patients) after 48 weeks, 93.8% (15 of 16 patients) after both 72 weeks and 96 weeks, 100.0% (14 of 14 patients) after both 120 weeks and 144 weeks, and 93.3% (14 of 15 patients) after 168 weeks.

According to the clinical study report of the previous study, the percentages of patients showing 30%, 50% and 70% improvement at 12 weeks after the start of treatment were 94.7% (18 of 19 patients), 94.7% (18 of 19 patients) and 57.9% (11 of 19 patients), respectively. At 24 weeks after the start of treatment, the percentages of patients showing 30%, 50% and 70% improvement were all 94.1% (16 of 17 patients); thus, not only were the percentages of 30% and 50% improvement greater than 90%, the percentage of 70% improvement was also greater than 90%. In subsequent long-term treatment as well, percentages of about 90% or higher were maintained for 30%, 50% and 70% improvement.

Table 17. Time Courses of Percentage of Patients Showing 30%, 50% and 70% Improvement in the JIA Core Set

Visit	n	Responder	Non-Responder	Response Rate(%)	95% CI Lower - Upper
JIA30					
WEEK 24	17	16	1	94.1	71.3 - 99.9
WEEK 48	17	17	0	100.0	80.5 - 100.0
WEEK 72	16	16	0	100.0	79.4 - 100.0
WEEK 96	16	16	0	100.0	79.4 - 100.0
WEEK 120	14	14	0	100.0	76.8 - 100.0
WEEK 144	14	14	0	100.0	76.8 - 100.0
WEEK 168	15	15	0	100.0	78.2 - 100.0
JIA50					
WEEK 24	17	16	1	94.1	71.3 - 99.9
WEEK 48	17	16	1	94.1	71.3 - 99.9
WEEK 72	16	16	0	100.0	79.4 - 100.0
WEEK 96	16	16	0	100.0	79.4 - 100.0
WEEK 120	14	14	0	100.0	76.8 - 100.0
WEEK 144	14	14	0	100.0	76.8 - 100.0
WEEK 168	15	14	1	93.3	68.1 - 99.8
JIA70					
WEEK 24	17	16	1	94.1	71.3 - 99.9
WEEK 48	17	15	2	88.2	63.6 - 98.5
WEEK 72	16	15	1	93.8	69.8 - 99.8
WEEK 96	16	15	1	93.8	69.8 - 99.8
WEEK 120	14	14	0	100.0	76.8 - 100.0
WEEK 144	14	14	0	100.0	76.8 - 100.0
WEEK 168	15	14	1	93.3	68.1 - 99.8

N represents number of patients contributing to summary statistics.
n represents number of responders.

2.2.3.1. Discussion on Clinical Efficacy

The pivotal phase III study WA19977 consisted of 3 parts. An initial 16-week open label lead in period (Part I) is followed by a randomized double blind withdrawal phase for a maximum of 24 weeks. Part III, a 64 week open-label period to examine the long term use of tocilizumab on safety and efficacy is

currently ongoing. The design of this study is considered acceptable: the withdrawal phase enables to evaluate the efficacy in a controlled manner, while using an escape endpoint, reducing the exposure to poor response for a relative short period. The approach is in line with the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (CHMP/EWP/422/04).

Juvenile idiopathic arthritis is a heterogeneous group of disease, ILAR has introduced a new nomenclature and classified the disease and distinguishes 7 subgroups. The MAH included patients with active polyarticular juvenile idiopathic arthritis (RF-positive or RF negative pJIA, and extended oligoarticular arthritis) in the study. The 3 subgroups can be considers as homogenous population since the disease characteristics are similar.

Given the small numbers in the subsets, the data are pooled for analysis. This approach is consistent with the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (CHMP/EWP/422/04). The patients were divided into two body weight categories. TCZ was dosed according the body, patients weighing at least 30 kg received 8 mg/kg TCZ q4w; patients with a body weight below 30 kg were randomized to either 10 mg/kg or 8 mg/kg q4w.

The primary efficacy endpoint was the proportion of patients developing JIA ACR30 flare between Week 16 and Week 40 in patients receiving placebo and those receiving TCZ. The JIA ACR30 flares relative to week 16 in patients receiving TCZ was statistically significantly lower than the rate in patients receiving placebo (25.6% vs. 48.1%). The primary endpoint was met.

This result was supported by a predefined set of secondary analyses, controlling for multiple testing. To control for the type I error rate, the secondary endpoints were tested in a hierarchical fixed sequence approach. The chain of statistical significance in the hierarchical testing of secondary endpoints was broken after the seventh of 13 endpoints. The patients improved rapidly following dosing with TCZ

Thus it can be considered that the results demonstrated a clinically relevant effect in patients treated with TCZ.

In Part I of the study the onset of efficacy was observed after the first dose of TCZ.

There was no gender effect on the efficacy observed.

A smaller proportion of patients aged ≤7 years achieved JIA ACR 30/50/70 responses than patients aged ≥ 8 years, while proportions of patients achieving JIA ACR90 are comparable in all age groups. This observation is not unexpected and is partly due to the lower exposure to TCZ in younger patients. Patients with younger age had lower body weight and thus had lower drug exposure and associated lower efficacy scores. There was a trend of a better response in children with body weight of less than 30 kg receiving the higher dose of 10 mg/kg, supporting the proposed dose of 10 mg/kg in lower weight children. Generally the <30 kg treatment groups included a lower proportion of RF positive patients than the ≥ 30 kg group. The MAH argued that the observed difference in the different age groups might also be linked to the fact that the proportions of rheumatoid factor (RF) positive and RF negative patients differed between treatment groups. This claim is not supported by the data so far. The MAH will initiative a collecting of long term efficacy and safety data in pJIA treatment through a registry also covering the efficacy of 10 mg/kg for patients <30 kg. This paediatric registry is described in the risk management plan.

The MAH provided a subgroup analysis of JIA ACR response rates between RF positive and RF negative patients. The efficacy of TCZ in terms of JIA response rates was generally similar regardless of the patients' RF status; however the groups are too small to detect meaningful differences.

During the evaluation the MAH was requested to provide subgroup analysis for patients with extended oligoarthritis. According to the ILAR diagnostic criteria oligoarticular JIA is characterized by 1 to 4 active joints in the first six months of disease. Oligoarticular JIA that does not progress after 6 months is termed persistent oligoarticular JIA and is not included in WA19977. If there is progression of oligoarticular JIA to affect ≥5 joints after six months it is classified as extended oligoarticular JIA (eoJIA) while pJIA is characterized by ≥5 joints in the first six months of disease. After 6 months of disease (the minimum disease duration required for entry into WA19977) the polyarticular course of eoJIA is no different to that observed in patients originally diagnosed with pJIA. Patients with oligoarticular disease onset, including eoJIA, are almost exclusively RF- at diagnosis and maintain their RF- status throughout their disease course.

Therefore the analysis of efficacy by RF status captures eoJIA patients along with RF- pJIA patients in the RF population.

Of the 188 patients enrolled in WA19977 54 were RF+, 126 were RF- and no RF status was recorded in 8 patients.

Figure 1. JIA ACR Responses at Week 16 by Rheumatoid Factor at Baseline

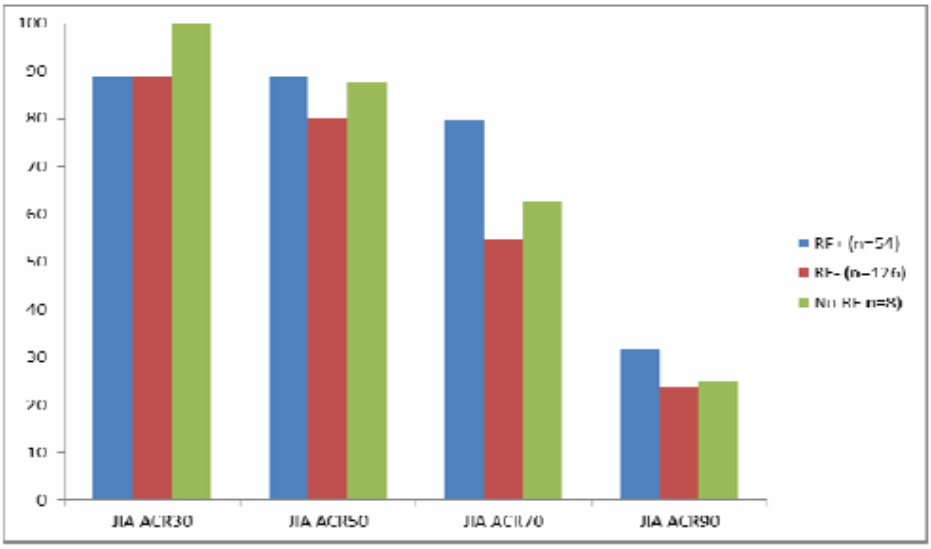
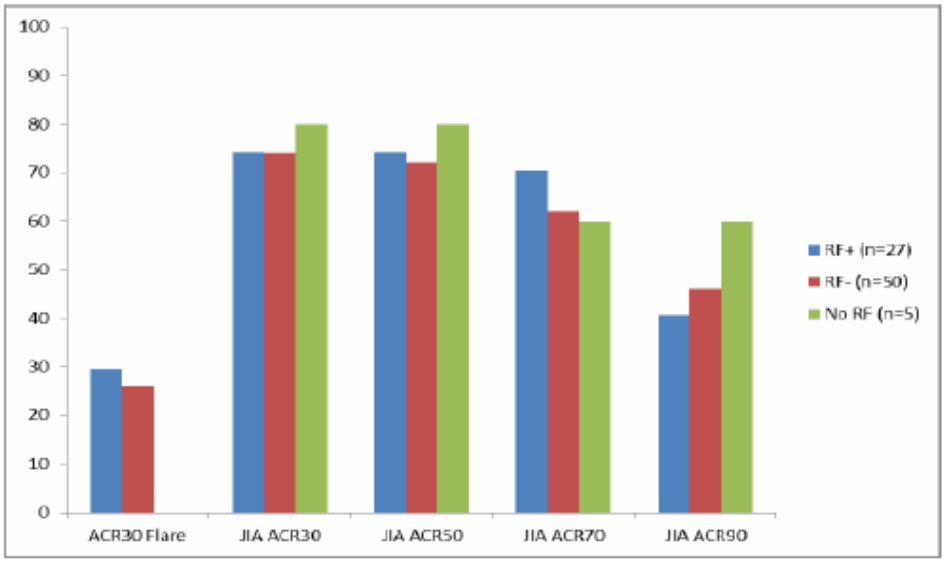


Figure 6. JIA ACR30 Flare and Week 40 JIA ACR Responses in Patients Randomised to TCZ by Rheumatoid Factor at Baseline



The MAH interpretation of these data is that patients with an initial diagnosis of eoJIA or RF- pJIA are at neither a therapeutic advantage or disadvantage relative to those patients with an initial eoJIA or RF- pJIA. The MAH's arguments were considered acceptable by the CHMP.

Study WA19977 was designed to evaluate a population of patients with an inadequate response to MTX due to lack of efficacy or toxicity, patients were required either not be taking MTX, or be on a stable dose of MTX for 12 weeks prior to baseline. Patients on MTX had lower JIA ACR flare rates and higher JIA ACR response rates regardless of assignment to TCZ or placebo treatment. It has been shown in a logistic regression analysis of JIA ACR30 flares that MTX use had a significant influence on the response independent of TCZ treatment. Patients taking concomitant MTX have better outcomes than those who do not, regardless of assignation to TCZ or placebo. Of note, in patients not taking MTX 53.3% of patients treated with TCZ achieved a JIA ACR70 response at week 40 compared with 23.5% of patients treated with placebo.

Oral corticosteroid use at baseline was also a stratification factor in the randomization of patients at Week 16, and patients were required to maintain oral corticosteroid use at a constant level until Week 40 unless a change was required for safety reasons. There was no consistent trend in the JIA ACR30 flare rate at Week 40 based on concurrent corticosteroid use, and the oral corticosteroid use term was not statistically significant in the confirmatory logistic regression analysis. The interaction of TCZ with oral corticosteroid use was assessed and was found non-significant (p-value 0.3267), suggesting that the benefit from TCZ was independent of corticosteroid. However this conclusion might be hampered by the small sample size.

The inclusion criteria specified that disease had to have been present for 6 month or more with still 5 active joints. Consequently patients with disease duration from 6 month to several years are included in the study. As mentioned by the MAH treatment outcome was poorer in children with disease duration of more than 2 years. During the evaluation the MAH was requested to provide a separate analysis of the efficacy data in those receiving treatment late versus earlier in the disease course. Effective control of JIA disease activity early in the disease course is being advocated as a way of improving longer term outcomes (1). While the cut-off for distinguishing early vs. late disease is somewhat arbitrary, the MAH considers a 2 year cut-off to be reasonable since it distinguishes the diagnosis, assessment and first line therapy phases from the second and further line phases of patient management.

JIA ACR 30/50/70/90 responses at Week 16 were summarised by the subgroups of patients with disease duration <2 years and ≥2 years. The data are provided in the table below.

Table 18. Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16, by Duration of Disease at Baseline (Lead in Phase Study Part I, ITT Population)

Duration of Disease <2 Years	TCZ 10 mg/kg (<30kg) (N=11)	TCZ 8 mg/kg (<30kg) (N=11)	TCZ 8 mg/kg (>=30kg) (N=40)	ALL TCZ (N=62)
JIA ACR30	10 (90.9%)	9 (81.8%)	38 (95.0%)	57 (91.9%)
JIA ACR50	9 (81.8%)	9 (81.8%)	35 (87.5%)	53 (85.5%)
JIA ACR70	8 (72.7%)	8 (72.7%)	30 (75.0%)	46 (74.2%)
JIA ACR90	5 (45.5%)	5 (45.5%)	14 (35.0%)	24 (38.7%)
Duration of Disease >=2 Years	TCZ 10 mg/kg (<30kg) (N=24)	TCZ 8 mg/kg (<30kg) (N=23)	TCZ 8 mg/kg (>=30kg) (N=79)	ALL TCZ (N=126)
JIA ACR30	21 (87.5%)	17 (73.9%)	73 (92.4%)	111 (88.1%)
JIA ACR50	19 (79.2%)	15 (65.2%)	69 (87.3%)	103 (81.7%)
JIA ACR70	14 (58.3%)	6 (26.1%)	51 (64.6%)	71 (56.3%)
JIA ACR90	6 (25.0%)	3 (13.0%)	16 (20.3%)	25 (19.8%)

At the end of Part I of the study JIA ACR response rates were numerically lower in patients with disease duration of ≥2 years.

JIA ACR 30/50/70/90 responses at Week 40 and JIA ACR30 Flare rates were also presented by the subgroups of patients with disease duration <2 years and ≥2 years. The data are provided in the table below.

Table 19. Proportion of Patients with JIA ACR30 Flare and Proportion of Patients with JIA ACR 30/50/70/90 Responses at Week 40, by Duration of Disease at Baseline (Lead in Phase Study Part I + Withdrawal Phase Study Part II, ITT Population – Study Part II)

	All Placebo (N=81)		All TCZ (N=82)	
	Duration of Disease <2 Years (N=28)	Duration of Disease >= 2 Years (N=53)	Duration of Disease <2 Years (N=26)	Duration of Disease >= 2 Years (N=56)
ACR30 Flare	12 (42.9%)	27 (50.9%)	4 (15.4%)	17 (30.4%)
JIA ACR30	16 (57.1%)	28 (52.8%)	22 (84.6%)	39 (69.6%)
JIA ACR50	15 (53.6%)	27 (50.9%)	21 (80.8%)	39 (69.6%)
JIA ACR70	14 (50.0%)	20 (37.7%)	21 (80.8%)	32 (57.1%)
JIA ACR90	10 (35.7%)	9 (17.0%)	20 (76.9%)	17 (30.4%)

At the end of Part II of the study JIA ACR 30/50/70/90 response rates were lower in patients with disease duration of ≥2 years. Similarly, JIA ACR30 Flare rates were higher in patients with disease duration of ≥2 years. Efficacy was better in TCZ patients compared to Placebo patients, regardless of disease duration. Due to smaller sample sizes, data should be interpreted with caution. Nevertheless, these data are consistent with the notion that effective treatment earlier in the course of disease can contribute to better efficacy outcomes.

No comparative analyses were provided on therapeutic efficacy of TCZ and other biologic for treatment of patients with pJIA used in MTX combination or as monotherapy in the submitted documentation. The MAH was requested during the evaluation to provide such comparative analyses in which at least data of published clinical studies would be used as the source of information.

At the time of submission, three biologics are approved for use in pcJIA in the EU: etanercept, adalimumab and abatacept. Of these three both etanercept and adalimumab are TNF inhibitors while abatacept is T-cell activation inhibitor (through action on CD28). Abatacept and adalimumab are approved for use in combination with methotrexate (MTX) in MTX-IR patients and as monotherapy in patients unable to tolerate MTX. Etanercept is approved for monotherapy use only.

The pcJIA studies for all three molecules were of a randomized withdrawal design similar to that utilized in WA19977 although the duration of study phases and study populations differed between the studies (see table below).

Table 20. Summary of Studies in pcJIA

	Study Drug	Trial Duration	Patient and Disease Characteristics	No. Patients Randomized	JIA ACR Response: Lead-In Phase	Flare Rate:	JIA ACR Response: Withdrawal Period (Active/PBO)	Qualifications
Lovell 2000	Etanercept	Phase 1: 12 weeks Phase 2: 16 weeks	Children 4-17 years with MTX-IR active JIA (oligoarticular, polyarticular, systemic)	Phase 1: 69 Phase 2: 51	ACR30: 76% ACR50: 64% ACR70: 36%	ETN 28% PBO 81%	ACR50: 72%/23% ACR70: 44%/19%	Enrolled systemic patients. Allowed flare patients to be counted as ACR responders. Monotherapy only.
Ruperto 2008	Abatacept	Phase 1: 16 weeks Phase 2: 24 weeks	Children 6-17 years with DMARD-IR active JIA (oligoarticular, polyarticular, systemic)	Phase 1: 190 Phase 2: 122	ACR30: 65% ACR50: 50% ACR70: 28% ACR90: 13%	ABA 20% PBO 53%	ACR30: 82%/69% ACR50: 77%/52% ACR70: 53%/31% ACR90: 40%/11%	Enrolled systemic patients. Allowed flare patients to be counted as ACR responders. Mono and combination therapy.
Lovell 2008*	Adalimumab	Phase 1: 16 weeks Phase 2: 32 weeks	Children 4-17 years with MTX-IR and MTX-naive NSAID-IR active pcJIA (extended oligoarticular and polyarticular)	Phase 1: 85** Phase 2: 75**	ACR30: 94% ACR50: 91% ACR70: 71% ACR90: 28%	ADA 37% PBO 65%	ACR30: 63%/38% ACR50: 63%/38% ACR70: 63%/27% ACR90: 42%/27%	Flare patients categorized as ACR non-responders. Data from patients receiving concurrent MTX presented.
CHERISH 2012	Tocilizumab	Phase 1: 16 weeks Phase 2: 24 weeks	Children 2-7 years with MTX-IR active pcJIA (extended oligoarticular and polyarticular)	Phase 1: 188 Phase 2: 163	ACR30: 89% ACR50: 83% ACR70: 62% ACR90: 26%	TCZ 26% PBO 48%	ACR30: 74%/54% ACR50: 73%/52% ACR70: 65%/42% ACR90: 45%/23%	Flare patients categorized as ACR non-responders. Mono and combination therapy.

*Data was presented as monotherapy and MTX combination therapy. Given the fact that the abatacept and tocilizumab data is not presented in this way, only the results of the MTX combination population are presented here. Details of monotherapy efficacy are presented in the manuscript listed in the references.
** Patients that received MTX + adalimumab only

Due to the fact that the etanercept and abatacept studies enrolled patients with all subtypes of JIA, including sJIA, and due to differences in the statistical methodologies utilized in both studies, the MAH considers it inappropriate to directly compare the results of these two studies with TCZ study WA19977. The etanercept and abatacept studies allowed patients who flared during the double blind phase to be counted as JIA ACR responders while WA19977 (and the Lovell at al. adalimumab study) counted flare patients as JIA ACR non-responders, regardless of JIA ACR response achieved prior to flare. Despite the greater similarities in study design and statistical analyses between WA19977 and the adalimumab study the MAH considers it methodologically flawed to make direct comparisons between these studies. Firstly, the adalimumab study included MTX naïve patients with less severe disease whereas all of the patients enrolled in WA19977 had prior MTX exposure and had more severe disease. Secondly, 32% of patients enrolled in WA19977 had a prior inadequate response to another biologic drug. No such prior biologic exposure in the adalimumab population was reported by Lovell et al. (2008) which could lead to the conclusion that the WA19977 patient population may also have more refractory disease compared to those in the adalimumab study. These patients tend to have higher flare rates and lower JIA ACR response rates in comparison with biologic-naïve patients. Efficacy of TCZ stratified by prior biologic use at both Week 16 and Week 40 has been provided in the original TCZ submission but is not available in the Lovell et al publication. Thirdly, the all-TCZ summary data includes the 8 mg/kg (<30 kg) dose group which showed suboptimal efficacy relative to the other two doses investigated whereas the adalimumab study was a non-doseranging study in which all patients received the recommended dose.

Nevertheless, on the basis of an indirect and qualitative comparison of the data presented above it is the opinion of the MAH that tocilizumab is at least as effective as adalimumab, etanercept and abatacept in pcJIA patients.

The MAH's argumentation is considered acceptable. Unfortunately there are no comparative data available of face to face trials biological products in patients with pJIA available for the time being. Still it can be established, based on the data presented by the MAH, that the therapeutic effects which can be achieved by TCZ in patients with pJIA are similar to those produced by adalimumab, etanercept or abatacept, as stated by the MAH.

The MAH was requested during the evaluation to propose how efficacy and safety of re-treatment with TCZ will be evaluated in patients who are experiencing flares during treatment holidays.

The randomized withdrawal design of study WA19977 allows for assessment of efficacy and safety in patients randomized to placebo in part II. Those that did not flare were retreated with TCZ in part III (from week 40) whilst those that experienced a JIA ACR30 flare during part II were re-treated with TCZ as escape therapy. Part III of the study is currently ongoing.

Of the 188 patients that were enrolled in study WA19977 166 entered the double-blind withdrawal period with 82 TCZ; 84 randomized with placebo. Of 81 out of these 84 placebo patients in the ITT Population, 39 (48.1%) experienced a JIA ACR30 flare while off TCZ between Week 16 and Week 40 and re-initiated TCZ treatment. In terms of the efficacy of re-treatment with TCZ, the MAH will provide the final study report after completion of part III of study WA19977. The submission of the final study report for study WA19977 is part of the RMP

2.2.3.2. Conclusions on Clinical Efficacy

In the pivotal phase III study WA19977, the primary efficacy endpoint was the proportion of patients developing JIA ACR30 flare between Week 16 and Week 40. Patients receiving placebo and those receiving TCZ were compared. Three subsets of the JIA population were included in the study: RF-positive or RF negative pJIA, and extended oligoarticular arthritis.

The JIA ACR30 flares relative to week 16 in patients receiving TCZ was statistically significantly lower than the rate in patients receiving placebo (25.6% vs. 48.1%). The primary endpoint was met.

This result was supported by a predefined set of secondary analyses, controlling for multiple testing. To control for the type I error rate, the secondary endpoints were tested in a hierarchical fixed sequence approach. The chain of statistical significance in the hierarchical testing of secondary endpoints was broken after the seventh of 13 endpoints. The proportion of patients with JIA ARC/30/50/70 improvement was statistical significant higher in the TCZ group than in the placebo group. Change from baseline in number of active joints, in Physician's global assessments VAS and in pain VAS also demonstrated statistical significant superiority of TCZ over placebo.

The treatment effect is independent of initial diagnosis of eoJIA or RF- pJIA. Furthermore, the data are consistent with the notion that effective treatment earlier in the course of disease can contribute to better efficacy outcomes. Although patients taking concomitant MTX have generally better outcomes adequate response was also demonstrated for patients treated with TCZ without MTX compared to placebo-treated patients. Available data suggests that the treatment effect from TCZ is independent of corticosteroid use although the small sample size was too small to draw firm conclusions. Overall, tocilizumab appears to be at least as effective as adalimumab, etanercept and abatacept in pcJIA patients even though unfortunately no direct comparative data of different biological products in patients with pJIA are available for the time being. Information on re-treatment after flare will be coming from part III of the ongoing study.Thus it can be considered that the results demonstrated a significant clinical benefit in patients with RF-positive or RF negative pJIA, and extended oligoarticular arthritis.

Impairment of growth is a common problem in juvenile rheumatoid arthritis, particularly in children with active disease. So far no data on the potential impact on TCZ therapy on growth retardation of in the paediatric population are available. Furthermore there is evidence that JIA is associated with increased risk for atherosclerosis, yet the data are scare. The MAH will initiative a collecting of long term efficacy and safety data in pJIA treatment through a registry also covering the impact of TCZ therapy on the increased risk of atherosclerosis and growth development, respectively. This paediatric registry is described in the risk management plan.

2.2.4. Clinical safety aspects

Patient exposure

The database supporting the safety of TCZ for treatment of pJIA includes the pivotal phase III study (WA19977), and is supported by the data from studies MRA318JP and MRA319JP.

In addition post-marketing safety data with TCZ for pJIA patients are provided in a tabulated overview in comparison with the paediatric data.

Study WA1997 consists of thee part, a 16-week active-treatment lead-in period (Part I), a 24-week double-blind, placebo-controlled withdrawal period (Part II) followed by a 64-week, open-label, extension period (Part III). During Part I 177/188 patients (94%) received all four planned TCZ infusions and during Part II, 57/82 patients (70%) and 43/81 (53%) received all six scheduled infusions of TCZ and placebo, respectively. At the time of the data cut, the median exposure to TCZ across Parts I, II, and III was 48 weeks (0.92 years). The total duration of exposure to TCZ was 184.4 patient-years; this is the total exposure used to determine the rate of adverse events per 100 patient years

All 188 patients had at least 1 safety assessment following the first infusion of TCZ and were therefore included in the safety population, which was used in the analyses of safety data. The ITT and safety populations were therefore equivalent.

The safety results in this report have been presented using the all exposure population; this includes all the patients until their last visit before 04 November 2011.

Table 21. Summary of Exposure to Study Drug and Duration in Study

stdl_durexp_ae Exposure to TCZ and Duration in Study (All Exposure, Safety Population)
Protocol(s): J19977A
Analysis: SAFETY Center: ALL CENTERS

	TCZ 10 MG/KG (<30KG)	TCZ 10 MG/KG to TCZ 8 MG/KG (<30KG)	TCZ 8 MG/KG (<30KG)	TCZ 8 MG/KG (>=30KG)	ALL TCZ
	N = 28	N = 7	N = 34	N = 119	N = 188
Exposure to TCZ (Years)					
Mean	0.83	1.24	0.72	1.01	0.94
SD	0.472	0.289	0.478	0.480	0.487
SEM	0.089	0.109	0.082	0.044	0.036
Median	0.83	1.29	0.77	0.99	0.92
Min-Max	0.2 - 1.7	0.8 - 1.6	0.0 - 1.8	0.0 - 1.8	0.0 - 1.8
Sum	23.3	8.7	24.6	120.3	176.9
n	28	7	34	119	188
Duration in Study (Years)					
Mean	0.88	1.24	0.80	1.04	0.98
SD	0.424	0.289	0.416	0.453	0.449
SEM	0.080	0.109	0.071	0.042	0.033
Median	0.85	1.29	0.81	1.02	0.93
Min-Max	0.3 - 1.7	0.8 - 1.6	0.2 - 1.8	0.1 - 1.9	0.1 - 1.9
Sum	24.7	8.7	27.1	123.9	184.4
n	28	7	34	119	188

n represents number of patients contributing to summary statistics.
Sum is across all patients in the treatment group.
SD = Standard Deviation. SEM = Standard Error of the Mean.
Data on Placebo treatment received in the study part II withdrawal phase is excluded.
For treatment groups the body weight category at Baseline is indicated in ( ).
DM11 23JAN2012:18:00:51

Adapted from Output std1_durexp_ae. page 1272

Adverse events

Table 22. Summary of Adverse Events with an Incidence of ≥5% in the All exposure population by Preferred Term and Study Drug (Safety Population)

stae13_ae Adverse Events by Preferred Term (All Exposure, Safety Population)
Protocol(s): J19977A
Analysis: SAFETY Center: ALL CENTERS
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Adverse Event	TCZ 10 MG/KG (<30KG) N = 28 No. (%)	TCZ 10 MG/KG to TCZ 8 MG/KG (<30KG) N = 7 No. (%)	TCZ 8 MG/KG (<30KG) N = 34 No. (%)	TCZ 8 MG/KG (>=30KG) N = 119 No. (%)	ALL TCZ N = 188 No. (%)
JUVENILE ARTHRITIS	6 (21.4)	2	6 (17.6)	35 (29.4)	49 (26.1)
NASOPHARYNGITIS	6 (21.4)	-	5 (14.7)	28 (23.5)	39 (20.7)
HEADACHE	3 (10.7)	-	5 (14.7)	18 (15.1)	26 (13.8)
UPPER RESPIRATORY TRACT INFECTION	2 (7.1)	-	3 (8.8)	14 (11.8)	19 (10.1)
COUGH	2 (7.1)	2	3 (8.8)	11 (9.2)	18 (9.6)
PHARYNGITIS	3 (10.7)	-	2 (5.9)	12 (10.1)	17 (9.0)
NAUSEA	-	-	2 (5.9)	14 (11.8)	16 (8.5)
DIARRHOEA	1 (3.6)	-	2 (5.9)	11 (9.2)	14 (7.4)
RHINITIS	2 (7.1)	1	4 (11.8)	7 (5.9)	14 (7.4)
VOMITING	1 (3.6)	1	3 (8.8)	9 (7.6)	14 (7.4)
ABDOMINAL PAIN	1 (3.6)	1	2 (5.9)	9 (7.6)	13 (6.9)
OROPHARYNGEAL PAIN	1 (3.6)	-	2 (5.9)	10 (8.4)	13 (6.9)
RASH	1 (3.6)	-	3 (8.8)	6 (5.0)	10 (5.3)

Investigator text for Adverse Events encoded using MedDRA version 14.1.
Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
Data on Placebo treatment received in the study part II withdrawal phase is excluded.
For treatment groups the body weight category at Baseline is indicated in ( ).
AE13_PDRD 23JAN2012:17:56:06

Table 23. Incidence of Adverse Events (≥15%) in the All Exposure Group by System Organ Class

System Organ Class	AE Incidence (%)	AE Rates Per 100 Patient-Years
Infections and infestations	61.2	163.7
Musculoskeletal and connective tissue disorders	34.0	53.1
Gastrointestinal disorders	31.9	71.0
Skin and subcutaneous tissue disorders	22.3	33.1
Respiratory, thoracic and mediastinal disorders	21.3	36.9
Nervous system disorders	19.7	28.7
Injury, poisoning and procedural complications	16.5	22.2

Sources: stae11_ae page 1274 and staerate02_otrt_npbo_se_p123a page 1288

Serious adverse event / deaths / other significant events

Death

There were no deaths during the study.

Serious adverse events

Seventeen patients (9.0%) reported 22 SAEs with a rate of 12.5 SAEs per 100 patient-years (in the all exposure population).

The SOC that had the most patients reporting at least 1 SAE in the all exposure population was infections and infestations (9 patients [4.8%]), followed by injury, poisoning and procedural complications (3 patients [1.6%]).

The majority of SAEs were individual cases occurring in individual patients with the exceptions of pneumonia, bronchitis and cellulitis. Pneumonia was reported in 4 patients (3 patients receiving TCZ 8 mg/kg [≥30 kg] and 1 patient receiving TCZ 10 mg/kg [<30 kg]). Bronchitis was reported in 2 patients receiving TCZ 10 mg/kg (<30 kg) and cellulitis was reported in 2 patients receiving TCZ 8 mg/kg (≥30kg).

Individual serious cases of varicella, neck injury, synovial rupture, upper limb fracture, sclerosing cholangitis, hypertransaminasemia, back pain, osteoporosis, familial mediterranean fever, uveitis, constipation, benign intracranial hypertension, psychosomatic disease and urinary calculus were reported.

Of the 22 SAEs reported, 5 SAEs that occurred in 5 patients (2.7%) were considered remotely, possibly or probably related to study drug by the investigator. The 5 events reported were benign intracranial hypertension, uveitis, urinary calculus, pneumonia, and cellulitis.

Table 24. Serious Adverse Events by Preferred Team (Safety Population)

stael3_s_ae Serious Adverse Events by Preferred Term (All Exposure, Safety Population)
Serious Adverse Events
Protocol(s): J19977A
Analysis: SAFETY Center: ALL CENTERS
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Adverse Event	TCZ 10 MG/KG (<30KG) N = 28 No. (%)	TCZ 10 MG/KG to TCZ 8 MG/KG (<30KG) N = 7 No. (%)	TCZ 8 MG/KG (<30KG) N = 34 No. (%)	TCZ 8 MG/KG (>=30KG) N = 119 No. (%)	ALL TCZ N = 188 No. (%)
PNEUMONIA	1 (3.6)	-	-	3 (2.5)	4 (2.1)
BRONCHITIS	2 (7.1)	-	-	-	2 (1.1)
CELLULITIS	-	-	-	2 (1.7)	2 (1.1)
BACK PAIN	-	-	-	1 (0.8)	1 (0.5)
BENIGN INTRACRANIAL HYPERTENSION	-	-	-	1 (0.8)	1 (0.5)
CALCULUS URINARY	-	-	-	1 (0.8)	1 (0.5)
CHOLANGITIS SCLEROSING	-	-	-	1 (0.8)	1 (0.5)
CONSTIPATION	-	-	-	1 (0.8)	1 (0.5)
FAMILIAL MEDITERRANEAN FEVER	-	-	-	1 (0.8)	1 (0.5)
HYPERTRANSAMINASAEMIA	-	-	-	1 (0.8)	1 (0.5)
NECK INJURY	-	-	-	1 (0.8)	1 (0.5)
OSTEOPOROSIS	-	-	-	1 (0.8)	1 (0.5)
PSYCHOSOMATIC DISEASE	-	-	-	1 (0.8)	1 (0.5)
SYNOVIAL RUPTURE	-	-	-	1 (0.8)	1 (0.5)
UPPER LIMB FRACTURE	-	-	-	1 (0.8)	1 (0.5)
UVEITIS	-	-	1 (2.9)	-	1 (0.5)
VARICELLA	-	-	1 (2.9)	-	1 (0.5)

Investigator text for Adverse Events encoded using MedDRA version 14.1.
Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
Data on Placebo treatment received in the study part II withdrawal phase is excluded.
For treatment groups the body weight category at Baseline is indicated in ( ).
AE13 23JAN2012:17:56:04 (1 of 1)

Adverse events of special interest

Infections

Over half of the patients in the all-exposure population in study WA19977 had at least one infection AE (115/188 [61.2%]). With a total of 302 infection AEs, the rate of infections was 163.7 per 100 patient years.

The most common types of infections include infections of the upper respiratory tract or the ears. There was one case of a primary pulmonary tuberculosis infection in an endemic region.

Nine patients (4.8%) had a serious infection, including four with pneumonia, two each with bronchitis and cellulitis, and one with varicella (hospitalised with varicella pneumonitis). All infection SAEs resolved without squeal.

There was no indication that patients who received concomitant oral corticosteroids or MTX had an increased risk for infections.

Hypersensitivity reactions

In order to identify events that may indicate hypersensitivity, analyses of infusion related AEs were performed. Infusion-related AEs were defined as any AEs occurring during or within 24 hours after the infusion of TCZ and that were not judged 'unrelated' to treatment by the investigator.

A total of 40 events were reported in 33/188 patients (17.6%). The rate of infusion related AEs was 23.3 events per 100 patient years. The most frequent individual AE terms were dizziness, headache, and hypotension (each at a rate of 2.2 AEs per 100 patient-years). None of the events were serious, and no patient was withdrawn as a result of an infusion-related event.

There were no cases of anaphylaxis.

Gastrointestinal Perforations

There were no gastrointestinal perforations reported in the study.

Malignancies

There were no malignancies reported in study WA19977. A total of four events of papilloma were reported. All were described as warts.

Immunogenicity

Almost all patients (185/188 or 98.4%) were tested for screening assay at any time point. Of these, 20 patients (10.6%) had positive baseline anti-TCZ assay results, 3 patients (1.6%) had positive screening assay results post-baseline, and 1 patient (0.5%) had positive confirmation and neutralizing assay results post-baseline. This patient did not experience infusion reactions. The patient was withdrawn as she did not achieve a JIA ACR30 response at the end of Part I and was therefore not eligible to continue in Part II.

Laboratory findings

Neutropenia and abnormal neutrophil count

There were no neutropenia AEs reported during the study, however decreases in neutrophil counts were observed during the study.

Table 25. Summary of Worst CTC Grades for Neutrophil Count (Hypo) by Study Drug (Safety Population)

stswfrq01_cgp2_se_sw123_xpbo Worst CTC Grades in Study for Selected Laboratory Parameters (Hypo) by Visit (All Exposure, Safety Population)

	TCZ 10 MG/KG (<30KG) (N=28)	TCZ 10 MG/KG to TCZ 8 MG/KG (<30KG) (N=7)	TCZ 8 MG/KG (<30KG) (N=34)	TCZ 8 MG/KG (>=30KG) (N=119)	ALL TCZ (N=188)
Neutrophils					
Overall					
n	28	7	34	119	188
NORMAL	21 (75.0%)	6 (85.7%)	25 (73.5%)	77 (64.7%)	129 (68.6%)
GRADE -1	0 (0.0%)	1 (14.3%)	0 (0.0%)	13 (10.9%)	14 (7.4%)
GRADE -2	5 (17.9%)	0 (0.0%)	6 (17.6%)	27 (22.7%)	38 (20.2%)
GRADE -3	2 (7.1%)	0 (0.0%)	3 (8.8%)	1 (0.8%)	6 (3.2%)
GRADE -4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.5%)

Percentages are based on n.
Each visit includes patients with a non-missing assessment at the timepoint. Patients who previously withdrew are excluded.
At post-Baseline visits Only worst values within a time window per patient are summarized.
Overall does not include Baseline.
Local analysis is excluded when central analysis is available on the same day.
CTC V3.0. Grading is on untransformed data.
The mutually exclusive CTC grades are "normal", "grade -1", "grade -2", "grade -3" and "grade -4".
Data on Placebo treatment received in the study part II withdrawal phase is excluded.
For treatment groups the body weight category at Baseline is indicated in ( ).
Program : $PROD/cs11935j/stswfrq01.sas
Output : $PROD/cs11935j/j19977a/reports/stswfrq01_cgp2_se_sw123_xpbo.out
31JAN2012 17:07

Adapted from output $PROD/cs11935j/j19977a/reports/stswfrq01_cgp2_se_sw123_xpbo.out page

In two patients infections (both non-serious) were reported in a temporary relation with the neutropenia was reported (gastroenteritis [Patient 2496, TCZ 8 mg/kg, ≥30 kg] and tracheitis 3 days prior to the neutropenia [Patient 2611, TCZ 10 mg/kg, <30 kg). Both events were reported as unrelated to study drug and the patients continued in the study.

Platelet count

During study treatment, mean platelet counts decreased in most subgroups of patient. There were few bleeding events with the most common being epistaxis in 7 patients.

One non-serious event of vaginal haemorrhage described as pre-menstrual red spot occurred in patient with a platelet count of 114 × 109/L. No serious bleeding events were reported.

Hepatic events and liver function test parameters

One event with preferred term 'hepatotoxicity' was reported in one patient in the TCZ 8 mg/kg (≥30kg) group on day 357. The event was recorded as mild in intensity and was attributed to MTX therapy.

ALT values remained within the normal range throughout study treatment in 126/187 patients (67.4%). The highest CTC grade ALT elevation in the study was one grade 3 event in one patient. AST concentrations remained within the normal range throughout study treatment in 152/187 patients (81.3%). There was one shift to a grade 3 AST value in a patient who had a grade 2 baseline value. There was no shift in total bilirubin to grade 3 or 4 values.

Lipid parameters

In general, mean lipid parameters including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride concentrations were within normal ranges for the duration of the study. For total cholesterol and LDL-cholesterol, the highest post baseline values were >1.5-2 × ULN and were reported in 0.5% of patients each. There were no clinically relevant findings in other laboratory safety parameters.

Comparison of TCZ safety in PJIA, SJIA and adult RA patients

The overall safety profile of TCZ was similar between the paediatric pJIA and adult RA patients. There were some differences in rates of AEs per 100 PY by SOC. The most notable difference was the rate of infections, which was higher in the pediatric population (see table below). This was to be expected since the age of onset is much younger in pJIA, affecting a population more prone to infection. The rate of musculoskeletal and connective tissue disorders was also higher in pJIA when compared to adult RA. This is considered largely a result of the different study designs and reporting practices in the paediatric and adult clinical studies. As discussed above, the high number of events in this system organ class in study WA19977 was the result of AEs reported as "juvenile arthritis" (59 of 98 events; rate per 100 patient years: 32.0), which were attributed to flares of the underlying disease. In the adult RA studies, AEs of "rheumatoid arthritis" were reported at a lower rate (723/4824 events; rate per 100 patient years: 4.8) . The rate of SAEs was not higher in pJIA than in adult RA. The number of individual SAEs in study WA19977 was too small to make a meaningful comparison to the adult data.

Table 26. Comparison of TCZ safety in pJIA, sJIA and adult RA patients

	pJIA [a]	Adult RA [b]	sJIA [c]
Number of patients	N = 188	N = 4009	N = 112
Exposure (patient years)	184.44	14 993.56	202.03
Number of Patients / Events [Rate per 100 Patient Years]			
Any AE	159/885 [479.8]	3799/45198 [301.4] 95% CI [d]: [299.7,304.2]	111/1660 [821.7]
Infections and infestations	115/302 [163.7]	3077/14112 [94.1]	102/570 [282.2]
Gastrointestinal disorders	60/131 [71.0]	2072/5467 [36.5]	67/145 [71.8]
Musculoskeletal and connective tissue disorders	64/98 [53.1]	1871/4824 [32.2]	57/178 [88.1]
Skin and subcutaneous tissue disorders	42/61 [33.1]	1327/2462 [16.4]	51/117 [57.9]
Respiratory, thoracic and mediastinal disorders	40/68 [36.9]	1115/1959 [13.1]	50/97 [48.0]
AE leading to withdrawal	6/6 [3.3]	749/754 [5.0]	6/6 [3.0]
SAE	17/23 [12.5]	1255/2194 [14.6] 95% CI [d]: [14.0,15.3]	35/47 [23.3]
Serious infections and infestations	9/9 [4.9]	507/668 [4.5]	20/22 [10.9]
Serious injuries, poisoning, and procedural complic.	3/3 [1.6]	182/191 [1.3]	5/6 [3.0]
SAE of neoplasms benign, malignant, and unspecified	0	165/177 [1.2]	3/3 [1.5]
Serious GI disorders	1/1 [0.5]	154/184 [1.2]	2/2 [1.0]
Serious musculoskeletal and connective tissue disorders	1/2 [1.1]	141/158 [1.1]	1/1 [0.5]
Serious cardiac disorders	0	122/158 [1.1]	1/1 [0.5]
Serious hepatobiliary disorders	1/2 [1.1]	40/52 [0.3]	1/1 [0.5]
Deaths	0	85 [0.6]	3 [1.5]

AEs were coded using MedDRA version 14.0 for sJIA and adult RA data and version 14.1 for pJIA data; individual SOCs chosen based on frequency and/or clinical relevance.

[a] All-exposure population in study WA19977.

[b] Adult RA data pooled from studies WA17822, WA17823, WA17824, WA18062, WA18063, WP18663, WA18695, or WA18696; data cut April 1, 2011.

[c] Week 104 data from study WA18221.

[d] based on χ^2 distribution; CI not calculated for individual SOCs or for pJIA, sJIA data.

Data sources for Table 24 : pJIA: staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, staerate02_otrt_npbo_se_aewd_p123a, sldd01_ae.

Adult RA: STae_rategp_all, STae_rategp_s, STae_rategp_wd, STrate_dd, sBLA 125276/49.

sJIA: staerate02_otrt_2, staerate02_ser_2, staerate02_aewd_2, stddrate01_2, CSR WA18221.

The rate of AEs and SAEs in sJIA patients treated with TCZ in study WA18221 was higher than that observed in pJIA or in adult RA patients. This was also true for most SOCs. The systemic form of JIA involves additional complications that are less common in pJIA or adult RA, such as multi-organ involvement. Other factors contributing to the higher rates of AEs and SAEs observed in sJIA include the more systemic nature of this illness. The pattern of changes in laboratory data (neutrophils, platelets, AST, ALT and total bilirubin) was consistent with changes observed amongst the pJIA, adult RA and sJIA populations (see table below). The majority of shifts were to CTC Grade 1 or 2 classifications.

Table 27. Comparison of Safety Laboratory Data by Worst CTC Grade during Study in pJIA, Adult RA, and sJIA

		pJIA [a]	Adult RA [b]	sJIA
Neutrophils (low)	n	188	4002	112
	Normal	129 (68.6%)	2163 (54.0%)	48 (42.9%)
	CTC Grade -1	14 (7.4%)	871 (21.8%)	2 (1.8%)
	CTC Grade -2	38 (20.2%)	723 (18.1%)	34 (30.4%)
	CTC Grade -3	6 (3.2%)	212 (5.3%)	26 (23.2%)
	CTC Grade -4	1 (0.5%)	33 (<1%)	2 (1.8%)
Platelets (low)	n	188	4002	112
	Normal	172 (91.5%)	3245 (81.1%)	80 (71.4%)
	CTC Grade -1	13 (6.9%)	673 (16.8%)	30 (26.8%)
	CTC Grade -2	1 (0.5%)	52 (1.3%)	1 (0.9%)
	CTC Grade -3	1 (0.5%)	18 (<1%)	1 (0.9%)
	CTC Grade -4	1 (0.5%)	14 (<1%)	0
AST (high)	n	187	4002	112
	Normal	152 (81.3%)	1540 (38.5%)	59 (52.7%)
	CTC Grade 1	32 (17.1%)	2130 (53.2%)	44 (39.3%)
	CTC Grade 2	2 (1.1%)	294 (7.3%)	5 (4.5%)
	CTC Grade 3	1 (0.5%)	35 (<1%)	3 (2.7%)
	CTC Grade 4	0	3 (<1%)	1 (0.9%)
ALT (high)	n	187	4002	112
	Normal	126 (67.4%)	1057 (26.4%)	45 (40.2%)
	CTC Grade 1	52 (27.8%)	2149 (53.7%)	44 (39.3%)
	CTC Grade 2	8 (4.3%)	661 (16.5%)	13 (11.6%)
	CTC Grade 3	1 (0.5%)	129 (3.2%)	9 (8.0%)
	CTC Grade 4	0	6 (<1%)	1 (0.9%)
Total bilirubin (high)	n	187	4002	112
	Normal	160 (85.6%)	3335 (83.3%)	95 (84.8%)
	CTC Grade 1	14 (7.5%)	428 (10.7%)	8 (7.1%)
	CTC Grade 2	13 (7.0%)	236 (5.9%)	9 (8.0%)
	CTC Grade 3	0	2 (<1%)	0
	CTC Grade 4	0	1 (<1%)	0

[a] All-exposure population in study WA19977.
[b] Adult RA data pooled from studies WA17822, WA17823, WA17824, WA18062, WA18063, WP18663, WA18695, or WA18696; data cut April 1, 2011.
[c] Week 104 data from study WA18221.
Source: stswfrq01_cgp2_se_sw123_xpbo, STIb_gradtt_lab, stswfrq01_cgp2_2, stswfrq01_cgp1_2.

Discontinuation due to AES and dose interruptions

Seven patients were withdrawn from the study due to an AE. This included 1 patient who was withdrawn following an event reported as juvenile arthritis, which indicated that the reason to discontinue treatment in this patient was insufficient efficacy. One of the 7 patients was withdrawn

from treatment due to an event of gastroenteritis that started while the patient received placebo in Part II of the study.

Of the 7 events leading to withdrawal from study, 2 events (hypertransaminasemia and benign intracranial hypertension) were serious.

Dose interruption

In the all exposure population, 12.8% of patients experienced TCZ dose interruptions because of safety concerns. There was a higher incidence of AEs leading to dose interruptions in patients receiving TCZ 10 mg/kg (<30 kg) (28.6%) than patients receiving TCZ 8 mg/kg (<30 kg) (5.9%). The AEs under the SOC of infections and infestations were the leading cause of TCZ dose interruption (9.0%), followed by AEs under the SOC of musculoskeletal and connective tissue disorders (1.6%) and gastrointestinal disorders (1.1%).

Supportive Studies

Study MRA318JP

Thirty-eight adverse events occurred in 17 of the 19 patients (89.5%) who were included in the safety evaluation set. Thirty-six of the events were mild and 2 were moderate. None of the events was assessed as severe. The incidences by SOC were as follows: 12 events of infections and infestations in 11 patients (57.9%), 9 events of gastrointestinal disorders in 7 patients (36.8%), 5 events of injury, poisoning and procedural complications in 4 patients (21.1%), 4 events of skin and subcutaneous tissue disorders in 4 patients (21.1%), 2 events of investigations in 2 patients (10.5%) and 2 events of nervous system disorders in 1 patient (5.3%). For all of the other SOCs with adverse events, there was 1 event of each.

Twenty-one adverse drug reactions occurred in 13 of the 19 patients (68.4%). Twenty-one of the adverse drug reactions were mild. None was assessed as moderate or severe. The incidences by SOC were as follows: 10 events of infections and infestations in 10 patients (52.6%), 5 events of gastrointestinal disorders in 5 patients (26.3%), 3 events of skin and subcutaneous tissue disorders in 3 patients (15.8%) and 2 events of investigations in 2 patients (10.5%). For the other SOC with an adverse drug reaction, there was 1 event.

Adverse events (PT) with an incidence of ≥10% were upper respiratory tract infection (26.3%, 5 patients), nasopharyngitis (21.1%, 4 patients), diarrhoea (15.8%, 3 patients) and arthropod sting (10.5%, 2 patients).

Three serious adverse events occurred in 3 patients. Those events (PT) were gastroenteritis, gastroenteritis bacterial and sensory disturbance. The causal relationship to the investigational product was “unrelated” for gastroenteritis bacterial and “unlikely” for the other 2 events. The outcome was “improved” for sensory disturbance and “resolved/recovered” for the other 2 events.

None of the patients died and none was withdrawn from the study because of adverse events.

Twelve adverse events classified under the SOC infections and infestations occurred in 11 of the 19 patients (57.9%). Those (PT) with an incidence of ≥10% were upper respiratory tract infection (26.3%, 5 events) and nasopharyngitis (21.1%, 4 events).

Infusion reactions consisted of 1 event each of nausea (at 1st infusion) and dizziness (at 3rd infusion) in 2 patients (10.5%).

Changes in laboratory test values were within the reference range or were changes in the direction of normalisation, except for increased ALP. The only patients in whom laboratory test values changed by

two or more NCI-CTC grades were 1 patient for the neutrophil count and 2 patients for the lymphocyte count, and the change in the neutrophil count was transient. Adverse events involving laboratory test values were 1 event each of lymphocyte count decreased and blood urine present.

One of the patients became positive for anti-TCZ antibodies (neutralising antibodies) on the last test day.

There were no changes in vital signs.

Study MRA319JP

There were a total of 142 adverse events in all 19 patients (100.0%) in the safety evaluation. As for severity, 136 events were “mild”, five events were “moderate” and one event was “severe”. Occurrence of adverse events by system organ class (SOC) in order of incidence was as follows: “infections and infestations”, 60 events in 18 patients (94.7%); “gastrointestinal disorders”, 18 events in 12 patients (63.2%); “skin and subcutaneous tissue disorders”, 14 events in 12 patients (63.2%); “injury, poisoning and procedural complications”, 16 events in 10 patients (52.6%); “respiratory, thoracic and mediastinal disorders”, six events in six patients (31.6%); “immune system disorders” and “musculoskeletal and connective tissue disorders”, each five events in five patients (26.3%); “eye disorders”, five events in four patients (21.1%); “nervous system disorders”, five events in three patients (15.8%); “investigations”, three events in three patients (15.8%); and “blood and lymphatic system disorders” and “ear and labyrinth disorders”, each two events in two patients (10.5%). In the other SOCs, the incidence was less than 10%.

There were 100 adverse drug reactions in 18 of the 19 patients (94.7%). As for severity, 98 of the adverse drug reactions were “mild”, one was “moderate” and one was “severe”. Occurrence of adverse drug reactions by SOC was as follows: “infections and infestations”, 52 reactions in 17 patients (89.5%); “skin and subcutaneous tissue disorders”, 11 reactions in 10 patients (52.6%); “gastrointestinal disorders”, 13 reactions in nine patients (47.4%); “respiratory, thoracic and mediastinal disorders”, six reactions in six patients (31.6%); “immune system disorders”, five reactions in five patients (26.3%); “eye disorders”, four reactions in three patients (15.8%); “nervous system disorders” and “investigations”, each three reactions in three patients (15.8%); and “musculoskeletal and connective tissue disorders”, two reactions in two patients (10.5%). The incidence was less than 10% for the other SOCs.

In order of decreasing incidence, the events (PTs) with an incidence of at least 10% were nasopharyngitis, 78.9% (15 patients); pharyngitis, 42.1% (eight patients); gastroenteritis, upper respiratory tract infection and arthropod sting, 31.6% (six patients) each; seasonal allergy and eczema, 21.1% (four patients) each; bronchitis, impetigo, influenza, conjunctivitis allergic, upper respiratory tract inflammation, abdominal pain, diarrhoea, stomatitis and urticaria, 15.8% (three patients) each; and pneumonia, headache, rhinitis allergic, constipation, enterocolitis, musculoskeletal stiffness and joint sprain, 10.5% (two patients) each.

Six serious adverse events occurred in four patients. Those events (PTs) were gastroenteritis, influenza, pneumonia, gastroenteritis bacterial, myasthenia gravis and sensory disturbance. The causal relationship to TCZ was assessed as “unrelated” for influenza and gastroenteritis bacterial, “unlikely” for gastroenteritis and sensory disturbance, and “possibly” for pneumonia and myasthenia gravis. The outcome was “improved” for myasthenia gravis and “resolved/recovered” for the other five events.

There were no adverse events that resulted in death.

One adverse event, myasthenia gravis in one patient, resulted in withdrawal of the patient from the study; the causal relationship to TCZ was assessed as “possibly”.

There were 60 occurrences of adverse events classified as the SOC “infections and infestations” in 18 of the 19 patients (94.7%). Of those, the events with an incidence of at least 10% were as follows: nasopharyngitis, 78.9% (15 patients); pharyngitis, 42.1% (eight patients); gastroenteritis and upper respiratory tract infection, 31.6% (six patients) each; bronchitis, impetigo and influenza, 15.8% (three patients) each; and pneumonia, 10.5% (two patients) each.

There were two infusion reactions in two patients (10.5%); those events were nausea (at the first infusion) and dizziness (at the third infusion) in one patient each.

Except for elevation of ALP, the changes in laboratory test values were either within the normal range or tended toward normal. The laboratory test values whose NCICTC grade changed by two or more grades and the numbers of patients affected were as follows: neutrophil count, seven patients; lymphocyte count and total bilirubin level, two patients; and haemoglobin level, WBC count, ALP value and CK value, one patient. Of those, changes of three grades (Grade 0 to Grade 3) were seen for the neutrophil count and CK value in one patient each. The three-grade exacerbations of the neutrophil count and CK value were both transient.

Regarding anti-TCZ antibodies, one patient (5.3%) became positive for neutralizing antibodies before the fourth infusion; and positive for IgE antibodies after the fifth infusion 657 days after the fourth infusion; and was withdrawn from the study.

Regarding vital signs, large changes were not observed in blood pressure, pulse rate or body temperature.

Post-marketing data

Post-marketing data is available from several sources:

- Japanese post-marketing study ML21939 for pJIA
- Japanese post-marketing study ML21940 for sJIA
- Spontaneous reports received globally, including those from non-interventional studies for patient treated for pJIA, sJIA, JIA that are unspecified by classification, and in paediatric patients under the age of 18 years treated with tocilizumab for unknown indications.

Tocilizumab has a marketing license in Japan. Tocilizumab has been available for treatment of multicentric Castleman’s disease in Japan since 2005 through a closed distribution program, and for treatment of RA, pJIA and sJIA since April 2008.

The MAH provided updated post-marketing data through 31 July 2012.

Consistent with study WA19977, the most common types of SAEs reported were infections. The safety profile of TCZ in patients with pJIA remains unchanged from the profile presented in the original submission and is consistent with that expected for a biologic agent in the pJIA population.

Table 28. Updated Summary of the Numbers and Proportion of SAEs by SOC: 17 December 2011 Cut-Off Date

SOC	Spontaneous pJIA (%)	sJIA JPMS ML21940 (%)	Spontaneous sJIA (%)	Unspecified JIA[a] (%)	Unknown Indications (%)	Total (%)
Infections	6 (33.3%)	72 (32.0%)	23 (26.4%)	9 (12.0%)	0	110 (26.5%)
Gastrointestinal	1 (5.5%)	22 (9.8%)	6 (6.9%)	6 (8.0%)	1 (10.0%)	36 (8.7%)
Musculoskeletal	0	13 (5.8%)	5 (5.7%)	13 (17.3%)	0	31 (7.5%)
General	4 (22.2%)	7 (3.1%)	10 (11.5%)	9 (12.0%)	2 (20.0%)	32 (7.3%)
Investigations	1 (5.5%)	24 (10.7%)	4 (4.6%)	3 (4.0%)	0	32 (7.7%)
Neoplasms	0	23 (10.2%)	5 (5.7%)	1 (1.3%)	0	29 (7%)
Blood disorders	0	14 (6.2%)	4 (4.6%)	4 (5.3%)	0	22 (5.3%)
Respiratory	2 (11.1%)	9 (4.0%)	4 (4.6%)	4 (5.3%)	1 (10.0%)	20 (4.8%)
Nervous system	1 (5.5%)	9 (4.0%)	2 (2.3%)	3 (4.0%)	1 (10.0%)	16 (3.9%)
Skin disorders	1[b]	5 (2.2%)	2 (2.3%)	6 (8.0%)	0	14 (3.4%)
Vascular disorders	0	4 (1.8%)	2 (2.3%)	5 (6.7%)	1 (10.0%)	12 (2.9%)
Immune disorders	0	1 (0.44%)	6 (6.9%)	4 (5.3%)	0	11 (2.7%)
Injury & poisoning	0	9 (4.0%)	5 (5.7%)	2 (2.7%)	0	16 (3.9%)
Hepatobiliary	1 (5.5%)	7 (3.1%)	0	0	0	8 (1.9%)
Renal	0	5 (2.2%)	2 (2.3%)	0	3 (30.0%)	10 (2.4%)
Reproductive	0	0	0	1 (1.3%)	0	1 (0.2%)
Pregnancy	0	0	0	0	0	0
Metabolism	0	0	0	1 (1.3%)	0	1(0.2%)

Additional safety data from study WA19977 will be reviewed and summarized in the final clinical study report with the conclusions of part III of this study. The MAH will review safety data in the pJIA population as part of ongoing Pharmacovigillance as well as within the context of a post-marketing registry (paediatric patients is included as important missing information in the RMP).

The table below shows the distribution of spontaneous reports across the pJIA population, patients enrolled in the Chugai Japanese Post-Marketing Surveillance (JPMS) study ML21940, and spontaneous reports received across sJIA patients, patients treated for unspecified JIA conditions, and other paediatric patients <18 years of age treated for unknown indications.

Table 29. Cumulative Distribution of SAEs by Source and Indication

	pJIA Spontaneous	sJIA JPMS ML21940	Spontaneous sJIA	Unspecified JIA[a]	Unknown Indications	Total
No of SAEs	18 [a]	225	87	75	10	415
No of patients	11[b]	106	46	45	4	211
Age range (years)	3–37	0.33–34	1–46	2–70	11–37	0.33–70

[a] Includes spontaneous and other sources.

[b] Includes one patient with one event from a non-interventional study.

The events identified from the updated search, and the numbers and proportion of these events by system organ class (SOC) are summarized in the table below. Across all populations, the most common types of events reported in >5% of patients were infections (26.6%), followed by gastrointestinal disorders (8.7%), investigations (7.7%), musculoskeletal disorders (7.5%), general disorders (7.3%), neoplasms (7%), and blood disorders (5.3%). Among individual patient groups, the frequencies of these types of events varied from those seen across all populations.

Within the post-marketing SAEs previously presented, the most frequently reported events reported in > 5% of patients across all patient groups were similar to those in the updated data cut. The most common events were infections (30%), followed by investigations (11.2%), gastrointestinal disorders (8.9%), neoplasms (8.9%), musculoskeletal disorders (6.7%), blood disorders (5.8%), and general disorders (5.1%).

2.2.4.1. Discussion on Clinical Safety

Due to the design of study WA19977, the placebo controlled withdrawal part was preceded by a lead in phase were all subjects were treated with TCZ. Thus all patients were exposed to TCZ which precludes a comparative assessment of the safety data.

The safety of TCZ was previously assessed in the paediatric population in sJIA patients.

Study WA1997 did not reveal any new safety signal. The safety between the pJIA and sJIA patients is similar with a trend to lower AE rates in the pJIA population compared to the sJIA population. This could be explained through more severe diseased sJIA population.

The most frequent AEs occurring were juvenile arthritis (which were underlying disease flares reported as AEs), nasopharyngitis, headache, upper respiratory tract infection, cough, pharyngitis, nausea, diarrhoea, rhinitis, vomiting, abdominal pain, oropharyngeal pain, and rash. The most common types of infections were those typically seen in children i.e. infections of the upper respiratory tract or viral infections.

The rate of SAEs was similar in the pJIA and adult population but lower than in the sJIA population. Again, this could explain by the generally more severe diseased sJIA population.

One patient experienced uveitis under treatment with TCZ, which is a known complication for JRA. The impact on the prevention/outcome of uveitis under treatment with TCZ should be addressed in the post-marketing setting. The overall prevalence of uveitis is estimated to be around 10-15% in the JIA population, with a higher prevalence in the extended oligoarthritis subgroup (around 20%). Additional risk factors for the development of uveitis include female gender, a young age of diagnosis and ANA positive status (about 30%). Thus, in spite of the exclusion of patients with prior uveitis on the basis of slit-lamp examination at screening, the report of uveitis in the WA19977 study is not unexpected. However, the paucity of literature on the incidence of uveitis means that an analysis of the relationship between TCZ usage and uveitis using WA19977 data is not possible. The MAH is planning to record the occurrence of uveitis in pJIA patients treated with TCZ in the post-marketing setting in the context of a registry. Independently, an investigator sponsored trial (supported via a financial grant by the MAH) is planning to treat five patients with JIA and uveitis with open-label TCZ; the design of the trial will preclude the results from making definitive conclusions, and given the independence of the sponsor from the MAH, whether and when these data are collected is uncertain. The plan to record the occurrence of uveitis in pJIA patients treated with TCZ in the post-marketing setting in the context of a new paediatric registry is endorsed. As per the RMP, the MAH should submit the outline of the registry for review by the CHMP.

There was one case of a primary pulmonary tuberculosis infection in an endemic region. This is not unexpected for the product class.

One event with preferred term ‘hepatotoxicity’ was reported in one patient treated concomitant with MTX. The event was attributed to MTX therapy.

Hepatic transaminases remained within the normal range throughout study treatment in the majority of the patient. There was no shift in total bilirubin to grade 3 or 4 values. The rate of patients with normal liver enzymes was higher than in the adult study and in the sJIA population.

Three patients (1.6%) had positive screening assay results post-baseline, and 1 patient (0.5%) had positive confirmation and neutralizing assay results post-baseline without evidence of clinical consequence.

2.2.4.2. Conclusions on Clinical Safety

The safety profile of TCZ in the paediatric population with pJIA is comparable with the safety profile in the adult RA population. No new safety signals were identified. The rates of adverse events, including SAEs, infections, serious infections and haematological abnormalities e.g. neutropenia and thrombocytopenia are lower than in the sJIA population. This might be partly explained by the less diseased population.

The long term safety profile of TCZ in the paediatric population is currently limited. Additional data will be provided through the final report of the last part of study WA19977 (part III). Furthermore, the MAH was requested to initiate a new paediatric registry to collect long term efficacy and safety data in pJIA treatment. Both data colleactions are documented in the risk management plan.

2.3. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure which included a risk minimisation plan. The key principles of the existing education material have been updated to include the new pJIA indication.

Table 30. 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 (see Section **Error! Reference source not found.**) • 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, and interstitial lung disease) 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.
Serious infections (cont'd)		SPC Section 4.8 Undesirable effects Infections In the 6-month, controlled studies the rate of all infections reported with

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Identified risks		
		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. Interstitial Lung Disease: Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes. 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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Identified risks		
		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. pJIA: The rate of infections in the tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%).

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 What you need to know 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. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately. 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 Minimization Activities (Routine and Additional)
Identified risks		
Complications of diverticulitis (including GI perforation)	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme (see Section **Error! Reference source not found.**) • 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 What you need to know 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
Serious hypersensitivity	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme (see	**Routine risk minimization by means of labelling:** **SPC Section 4.4 Special warnings and precautions for use**

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Identified risks		
	Section **Error! Reference source not found.**) • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	*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 Minimization 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. pJIA: In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab all exposure population, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occuring during

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Identified risks		
		infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients, see section 4.8. No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported. **Patient Information Leaflet** Section 2 What you need to know 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. Alert card to inform patients, parents, caregivers, and health care providers that patients using RoActemra may develop allergic reactions during or after the infusion. Patients who develop allergic reations after the infusion should seek medical attention immediately.

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	Study ML25243 **Routine risk minimization by means of labelling:** **SPC section 4.4 Special warnings and**

<table>
<tr><th>Safety Concern</th><th>Proposed Pharmacovigilance Activities (Routine and Additional)</th><th>Proposed Risk Minimisation Activities (Routine and Additional)</th></tr>
<tr><td>Potential risks</td><td>of special interest will collect neutrophil data in cases of serious infection
• Ongoing clinical trial programme (see Section Error! Reference source not found.)
• Regular review by Roche Pharmacoepidemiology Board</td><td>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 and pJIA 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 absolute neutrophil count (ANC)
<table><tr><td>Laboratory Value (cells x 10^9/L)</td><td>Action</td></tr><tr><td>ANC > 1</td><td>Maintain dose</td></tr><tr><td>ANC 0.5 to 1</td><td>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</td></tr><tr><td>ANC < 0.5</td><td>Discontinue RoActemra</td></tr></table>
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</td></tr>
</table>

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
		clinical practice, see section 4.2.
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. pJIA: During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1 × 10^9/L occurred in 3.7% of patients. 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)

<table>
<tr><th>Safety Concern</th><th>Proposed Pharmacovigilance Activities (Routine and Additional)</th><th>Proposed Risk Minimisation Activities (Routine and Additional)</th></tr>
<tr><td colspan="3">Potential risks</td></tr>
<tr><td>Thrombocytopenia</td><td>• Routine pharmacovigilance
• Ongoing clinical trial programme (see Section Error! Reference source not found.)
• Regular review by Roche Pharmacoepidemiology Board</td><td>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 and pJIA 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
<table><tr><td>Laboratory Value (cells x 10^3/ µl)</td><td>Action</td></tr><tr><td>50 to 100</td><td>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</td></tr><tr><td>< 50</td><td>Discontinue RoActemra</td></tr></table></td></tr>
<tr><td>Thrombocytopenia (cont’d)</td><td></td><td>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</td></tr>
</table>

<table>
<tr><th>Safety Concern</th><th>Proposed Pharmacovigilance Activities (Routine and Additional)</th><th>Proposed Risk Minimisation Activities (Routine and Additional)</th></tr>
<tr><td>Potential risks</td><td></td><td></td></tr>
<tr><td></td><td></td><td>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 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.

In pJIA:
During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to ≤ 50 × 10^3/µL without associated bleeding events.</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 (see Section Error! Reference source not found.)
• 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 and pJIA 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</td><td>Dose modify concomitant MTX if</td></tr></table></td></tr>
</table>

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		

Limit of Normal (ULN)	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
> 3 to 5 x ULN (confirmed by repeat testing, see section 4.4) .	Interrupt RoActemra dosing until < 3 x ULN and follow recommendations for > 1 to 3 x ULN (described above) For persistent increases > 3 x ULN, discontinue RoActemra
> 5 x ULN	Discontinue RoActemra

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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
		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 and pJIA 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.
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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
		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. pJIA: During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥ 3xULN occurred in 3.7% and <1% of patients, respectively. **Patient Information Leaflet** Section 2 What you need to know 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 **Error! Reference source not found.**) • 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. pJIA: One patient in the 10 mg/kg < 30kg group developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.
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 **Error! Reference source not found.**) • Guided Questionnaires on implications of elevated lipids: ischaemic cardiovascular events (e.g., MI/acute coronary syndrome) and implications of elevated lipids: cerebrovascular events (e.g., stroke) • Regular review by Roche Pharmacoepidemiology Board • Rate of clinical events potentially related to atherogenesis (e.g. angina, MI, cerebrovascular accident) as a potential clinical manifestation of increased lipid levels will be monitored in the registry studies. The nature and rate of such events will be monitored and evaluated on the basis of reports to the:	**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. 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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
	o Routine pharmacovigilance o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	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.
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. **pJIA:** During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol >1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL >1.5-2 x ULN in one patient (0.5%). **Patient Information Leaflet** Section 2 What you need to know 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-	**Routine risk minimization by means of labelling:**

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
	marketing data) • Ongoing clinical trial programme (see Section **Error! Reference source not found.**) • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	**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 **Error! Reference source not found.**) • 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 **Error! Reference source not found.**) • 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 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 **Error! Reference source not found.**) • 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 and pJIA 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)

<table>
<tr><th>Safety Concern</th><th>Proposed Pharmacovigilance Activities (Routine and Additional)</th><th>Proposed Risk Minimisation Activities (Routine and Additional)</th></tr>
<tr><td>Potential risks</td><td></td><td>Low absolute neutrophil count (ANC)
<table><tr><td>Laboratory Value (cells x 10^9/L)</td><td>Action</td></tr><tr><td>ANC > 1</td><td>Maintain dose</td></tr><tr><td>ANC 0.5 to 1</td><td>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</td></tr><tr><td>ANC < 0.5</td><td>Discontinue RoActemra</td></tr></table>
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.</td></tr>
<tr><td>Neutropenia (cont’d)</td><td></td><td>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</td></tr>
</table>

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
		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. pJIA: During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1×10^9/L occurred in 3.7% of patients. 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)

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<tr><th>Safety Concern</th><th>Proposed Pharmacovigilance Activities (Routine and Additional)</th><th>Proposed Risk Minimisation Activities (Routine and Additional)</th></tr>
<tr><td colspan="3">Potential risks</td></tr>
<tr><td>Thrombocytopenia</td><td>• Routine pharmacovigilance
• Ongoing clinical trial programme (see Section Error! Reference source not found.)
• Regular review by Roche Pharmacoepidemiology Board</td><td>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 and pJIA 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
<table><tr><td>Laboratory Value (cells x 10^3/ µl)</td><td>Action</td></tr><tr><td>50 to 100</td><td>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</td></tr><tr><td>< 50</td><td>Discontinue RoActemra</td></tr></table></td></tr>
<tr><td>Thrombocytopenia (cont’d)</td><td></td><td>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</td></tr>
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<tr><td>Potential risks</td><td></td><td></td></tr>
<tr><td></td><td></td><td>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 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.

In pJIA:
During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to ≤ 50 × 10^3/µL without associated bleeding events.</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 (see Section Error! Reference source not found.)
• 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 and pJIA 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</td><td>Dose modify concomitant MTX if</td></tr></table></td></tr>
</table>

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		

Limit of Normal (ULN)	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
> 3 to 5 x ULN (confirmed by repeat testing, see section 4.4) .	Interrupt RoActemra dosing until < 3 x ULN and follow recommendations for > 1 to 3 x ULN (described above) For persistent increases > 3 x ULN, discontinue RoActemra
> 5 x ULN	Discontinue RoActemra

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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
		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 and pJIA 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.
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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
		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. pJIA: During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥ 3xULN occurred in 3.7% and <1% of patients, respectively. **Patient Information Leaflet** Section 2 What you need to know 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 **Error! Reference source not found.**) • 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. pJIA: One patient in the 10 mg/kg < 30kg group developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.
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 **Error! Reference source not found.**) • Guided Questionnaires on implications of elevated lipids: ischaemic cardiovascular events (e.g., MI/acute coronary syndrome) and implications of elevated lipids: cerebrovascular events (e.g., stroke) • Regular review by Roche Pharmacoepidemiology Board • Rate of clinical events potentially related to atherogenesis (e.g. angina, MI, cerebrovascular accident) as a potential clinical manifestation of increased lipid levels will be monitored in the registry studies. The nature and rate of such events will be monitored and evaluated on the basis of reports to the:	**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. 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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
	o Routine pharmacovigilance o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	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.
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. **pJIA:** During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol >1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL >1.5-2 x ULN in one patient (0.5%). **Patient Information Leaflet** Section 2 What you need to know 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-	**Routine risk minimization by means of labelling:**

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Potential risks		
	marketing data) • Ongoing clinical trial programme (see Section **Error! Reference source not found.**) • Regular review by Roche Pharmacoepidemiology Board • Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT)	**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 **Error! Reference source not found.**) • 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 **Error! Reference source not found.**) • 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 What you need to know 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 **Error! Reference source not found.**) • 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	**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

	investigated in the longterm extension. In addition, investigations into dose reductions / treatment interruptions will be reported in upcoming PSURs. • On-goingStudy WA19977 (pJIA) • The efficacy of 10 mg/kg dosing for patients weighing less than 30 kg, will be substantiated via a paediatric registry.This registry will also be used to capture the occurance of uveitis and growth impairment in pJIA patients treated with tocilizumab in a post marketed setting.	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 What you need to know 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 **Error! Reference source not found.**) • 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 What you need to know 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.
Effects during pregnancy (cont'd)		**Patient Information Leaflet** Section 2 What you need to know 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.** <u>Special populations</u> *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** <u>Special populations</u> *Hepatic impairment:* No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted. **Patient Information Leaflet** Section 2 What you need to know 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.

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** Special populations *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 What you need to know 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, sJIA or pJIA patients. RoActemra is not recommended for use with other biological agents. **Patient Information Leaflet** Section 2 What you need to know 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.

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 and pJIA 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 What you need to know 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, was of the opinion that Pharmacovigilance activities in addition to the use of routine Pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Submission of the final report (part III) of study WA19977.	10 July 2013
Submission of the draft protocol of the registry as proposed by the MAH, collecting long term efficacy and safety data in PJIA treatment. The registry will address, but not limited to, efficacy of 10 mg/kg for patients <30 kg; impact of the RF status on efficacy of TCZ therapy; impact of TCZ therapy on the increased risk of atherosclerosis in RA patients, impact on of TCZ therapy growth development, influence on the occurrence / treatment of uveitis.	12 June 2013

2.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed (new text shown as underlined, deleted text as ~~strikethrough~~):

Section 4.1 Therapeutic indications of the SmPC

RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Section 4.2 Posology and method of administration of the SmPC

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA ~~or~~ sJIA or pJIA. All patients treated with RoActemra should be given the Patient Alert Card.

[...]

pJIA patients
The safety and efficacy of RoActemra in children below 2 years of age has not been established.

No data are available.

The recommended posology is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 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 pJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect laboratory values in pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	**Action**
> 1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt RoActemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing until <3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue RoActemra. The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- 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 to > 1 x 10^9/ l resume RoActemra
ANC < 0.5	Discontinue RoActemra The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10^3/μl)	**Action**
50 to 100	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing When platelet count is > 100 x 10^3/μl resume RoActemra
< 50	Discontinue RoActemra. The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in pJIA patients.

Available data suggest that clinical improvement is observed within 12 weeks of initiation of treatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

[...]

Method of administration
After dilution, RoActemra for RA ~~and~~ sJIA and pJIA patients should be administered as an intravenous infusion over 1 hour.

RA ~~Patients, and~~ sJIA and pJIA Patients ≥ 30 kg
RoActemra should be diluted to a final volume of 100 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique.

For instructions on dilution of the medicinal product before administration, see section 6.6.

sJIA and pJIA Patients <30 kg
RoActemra should be diluted to a final volume of 50 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique.

Section 4.4 Special warnings and precautions for use of the SmPC

In sJIA and pJIA 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.

[…]

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

Combination with TNF antagonists
There is no experience with the use of RoActemra with TNF antagonists or other biological treatments for RA ~~or~~ sJIA or pJIA patients. RoActemra is not recommended for use with other biological agents.
[…]

Paediatric population

SJIA and pJIA Patients

Section 4.8 Undesirable effects of the SmPC

Paediatric population

The safety of toclizumab in the paediatric population in the sections on pJIA and sJIA below. In general, the ADRs in pJIA and sJIA patients were similar in type to those see in RA patients, see section 4.8.

The ADRs in the pJIA and sJIA patients treated with tocilizumab are described below and are presented in the Table 2 by system organ class and frequency categories, defined using the following convention: very common (≥ 1/10); common (≥1/100 to < 1/10) or uncommon (≥ 1/1,000 to <1/100)

Table 2: Summary of ADRs occurring in patients with sJIA or pJIA receiving tocilizumab as monotherapy or in combination with MTX.

SOC	PT	Frequency		
Infections and Infestations		Very Common	Common	Uncommon
	Upper Respiratory Tract Infections	pJIA, sJIA		
	Nasopharyngitis	pJIA, sJIA		
Gastrointestinal Disorders				
	Nausea		pJIA	
	Diarrhea		pJIA, sJIA	
General disorders and administration site conditions				
	Infusion related reactions		pJIA[1], sJIA[2]	
Nervous system disorders				
	Headache	pJIA	sJIA	
Investigations				
	Hepatic transaminases increased		pJIA	
	Decrease in neutrophil count	sJIA	pJIA	
	Platelet count decreased		sJIA	pJIA
	Cholesterol increased		sJIA	pJIA

1. Infusion related reaction events in pJIA patients included but were not limited to headache, nausea and hypotension
2. Infusion related reaction events in sJIA patients included but were not limited to rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache

pJIA Patients

The safety of tocilizumab in pJIA has been studied in 188 patients from 2 to 17 years of age. The total patient exposure was 184.4 patient years. The frequency of ADRs in pJIA patients can be found in Table 2. The types of ADRs in pJIA patients were similar to those seen in RA and sJIA patients, see section 4.8. When compared to the adult RA population, events of nasopharyngitis, headache, nausea, and decreased neutrophil count were more frequently reported in the pJIA population. Events of cholesterol increased were less frequently reported in the pJIA population than in the adult RA population.

Infections

The rate of infections in the tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%).

Infusion Reactions

In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab all exposure population, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occuring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients, see section 4.8.

No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.

Immunogenicity

One patient in the 10 mg/kg < 30kg group developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.

Neutrophils

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1×10^9/L occurred in 3.7% of patients.

Platelets

During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to $\leq 50 \times 10^3$/µL without associated bleeding events.

Hepatic transaminase elevations

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥3xULN occurred in 3.7% and <1% of patients, respectively.

Lipid parameters

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol >1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL >1.5-2 x ULN in one patient (0.5%).

sJIA Patients

The safety of tocilizumab in sJIA has been studied in 112 patients from 2 to 17 years of age. In the 12 week double-blind, controlled phase, 75 patients received treatment with tocilizumab (8 mg/kg or 12 mg/kg based upon body weight). After 12 weeks or at the time of switching to tocilizumab, due to disease worsening, patients were treated in the ongoing open label extension phase.

In general, the ADRs in sJIA patients were similar in type to those seen in RA patients, see section 4.8. The frequency of ADRs in sJIA patients can be found in Table 2. When compared to the adult RA population, patients with sJIA experienced a higher frequency of nasopharyngitis, decrease in neutrophil counts, hepatic transaminases increased, and diarrhea. Events of cholesterol increased were less frequently reported in the sJIA population than in the adult RA population.

Infections
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 ongoing 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 ongoing 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.

Infusion Reactions
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. One 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 up to and including the open label clinical trial.

Immunogenicity
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.

Neutrophils
During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below 1 x 10^9/l occurred in 7% of patients in the tocilizumab group, and no decreases 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.

Platelets
During routine laboratory monitoring in the 12 week controlled phase, 3% of patients in the placebo group and 1% in the tocilizumab group had a decrease in platelet count to ≤100 x 10^3/µl.

In the ongoing open label extension phase, decreases in platelet counts below 100 x 10^3/µl, occurred in 3% of patients in the tocilizumab group, without associated bleeding events.

Hepatic transaminase elevations
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.

Immunoglobuilin G
IgG levels decrease during therapy. A decrease to the lower limit of normal occurred in 15 patients at some point in the study.

Lipid parameters
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 none in the 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.

~~*SJIA Patients*~~
~~The safety of tocilizumab in sJIA has been studied in 112 patients from 2 to 17 years of age. In the 12 week double-blind, controlled phase, 75 patients received treatment with tocilizumab (8 mg/kg or 12 mg/kg based upon body weight). After 12 weeks or at the time of switching to tocilizumab, due to disease worsening, patients were treated in the ongoing open label extension phase.~~

~~In general, the ADRs in sJIA patients were similar in type to those seen in RA patients, see section 4.8.~~

~~*Infections*~~
~~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 ongoing 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 ongoing 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.~~

~~*Infusion Reactions*~~
~~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. One 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, diarrhoea, 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 up to and including the open label clinical trial.~~

~~*Immunogenicity*~~
~~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.~~

~~*Neutrophils*~~
~~During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below 1 x 10^9/l occurred in 7% of patients in the tocilizumab group, and no decreases 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.~~

~~*Platelets*~~

~~During routine laboratory monitoring in the 12 week controlled phase, 3% of patients in the placebo group and 1% in the tocilizumab group had a decrease in platelet count to ≤ 100 x 10^3/µl.~~

~~In the ongoing open label extension phase, decreases in platelet counts below 100 x 10^3/µl, occurred in 3% of patients in the tocilizumab group, without associated bleeding events.~~

~~*Hepatic transaminase elevations*~~
~~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.~~

~~*Immunoglobuilin G*~~
~~IgG levels decrease during therapy. A decrease to the lower limit of normal occurred in 15 patients at some point in the study.~~

~~*Lipid parameters*~~
~~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 none in the 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.~~

Section 5.1 Pharmacodynamic properties of the SmPC

PJIA Patients
Clinical efficacy
The efficacy of tocilizumab was assessed in a three-part study WA19977 including an open-label extension in children with active pJIA. Part I consisted of a 16-week active tocilizumab treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period (n=163), followed by Part III, a 64-week open-label period. In Part 1, eligible patients ≥ 30 kg received tocilizumab at 8 mg/kg IV every 4 weeksfor 4 doses. Patients < 30 kg were randomized 1:1 to receive either tocilizumab 8 mg/kg or 10 mg/kg IV every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16 compared to baseline were eligible to enter the blinded withdrawal period (Part II) of the study. In Part II, patients were randomized to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio, stratified by concurrent MTX use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR30 flare criteria (relative to Week 16) and qualified for escape to tocilizumab therapy (same dose received in Part I).

Clinical response
The primary endpoint was the proportion of patients with a JIA ACR30 flare at week 40 relative to week 16. Forty eight percent (48.1%, 39/81) of the patients treated with placebo flared compared with 25.6% (21/82) of tocilizumab treated patients. These proportions were statistically significantly different (p=0.0024).

At the conclusion of Part I, JIA ACR 30/50/70/90 responses were 89.4%, 83.0%, 62.2%, and 26.1%, respectively.

During the withdrawal phase (Part II), the percentage of patients achieving JIA ACR 30, 50, and 70 responses at Week 40 relative to baseline are shown in Table 7. In this statistical analysis, patients who flared (and escaped to TCZ) during Part II or who withdrew, were classified as non-responders. An additional analyses of JIA ACR responses, considering observed data at Week 40, regardless of flare status, showed that by Week 40, 95.1% of patients who had received continuous TCZ therapy, had achieved JIA ACR30 or higher.

Table 7. JIA ACR Response Rates at Week 40 Relative to baseline (Percentage of Patients)

Response Rate	Tocilizumab N=82	Placebo N=81
ACR 30	74.4%*	54.3%*
ACR 50	73.2%*	51.9%*
ACR 70	64.6%*	42.0%*

** p<0.01, tocilizumab vs. placebo*

The number of active joints was significantly reduced compared to baseline in patients receiving tocilizumab compared to placebo (adjusted mean changes of -14.3 vs -11.4, p=0.0435). The physician's global assessment of disease activity, as measured on a 0-100 mm scale, showed a greater reduction in disease activity for tocilizumab compared to placebo (adjusted mean changes of -45.2 mm vs -35.2 mm, p=0.0031).

The adjusted mean change in the pain VAS after 40 weeks of tocilizumab treatment was 32.4 mm on a 0-100 mm scale compared to a reduction of 22.3 mm for placebo patients (highly statistically significant; p=0.0076).

The ACR response rates were numerically lower for patients with prior biologic treatment as shown in Table 8 below.

Table 8. Number and Proportion of Patients with a JIA ACR30 Flare and Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 40, by Previous Biologic Use (ITT Population - Study Part II)

	Placebo		**All TCZ**	
Biologic Use	**Yes (N =**	**No (N =**	**Yes (N =**	**No (N =**
JIA ACR30 Flare	18 (78.3)	21 (36.2)	12 (44.4)	9 (16.4)
JIA ACR30 Response	6 (26.1)	38 (65.5)	15 (55.6)	46 (83.6)
JIA ACR50 Response	5 (21.7)	37 (63.8)	14 (51.9)	46 (83.6)
JIA ACR70 Response	2 (8.7)	32 (55.2)	13 (48.1)	40 (72.7)
JIA ACR90 Response	2 (8.7)	17 (29.3)	5 (18.5)	32 (58.2)

Patients randomized to tocilizumab had fewer ACR30 flares and higher overall ACR responses than patients receiving placebo regardless of a history of prior biologic use.

Section 5.2 Pharmacokinetic properties of the SmPC

PJIA Patients:
The pharmacokinetics of tocilizumab was determined using a population pharmacokinetic analysis on a database composed of 188 patients with pJIA.

The following parameters are valid for a dose of 8 mg/kg tocilizumab (patients with a body weight ≥ 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 29500 ± 8660 µg·hr/mL, 182 ± 37 µg/mL and 7.49 ± 8.20 µg/mL, respectively.

The following parameters are valid for a dose of 10 mg/kg tocilizumab (patients with a body weight < 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 23200 ± 6100 µg·hr/mL, 175 ± 32 µg/mL and 2.35 ± 3.59 µg/mL, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{min} for 10 mg/kg (body weight < 30 kg) and 8 mg/kg (body weight ≥ 30 kg) doses, respectively. No accumulation for C_{max} was observed.

In pJIA patients, the central volume of distribution was 50 ml/kg, the peripheral volume of distribution was 53 ml/kg, resulting in a volume of distribution at steady state of 103 ml/kg. The linear clearance estimated as a parameter in the population pharmacokinetic analysis was 0.146 ml/hr/kg.

The half life of tocilizumab in pJIA patients is up to 16 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 10 mg/kg for body weight < 30 kg) during a dosing interval at steady state.

Section 6.6 Special precautions for disposal and other handling of the SmPC

Use in the paediatric population

SJIA and pJIA Patients ≥30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 100 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.4 ml/kg**) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

SJIA Patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.6 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

PJIA Patients <30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.5 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

Section D. Conditions or restrictions with regard to the safe and effective use of the medicinal product of Annex II

- **Additional risk minimisation measures**
  - The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA and sJIA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:
  -
  - • Physician Information Pack
  - • Nurse Information Pack
  - • Patient Information Pack
  -
  - The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational material.
  -
  - The Physician Information pack should contain the following key elements:
  - • The Summary of Product Characteristics
  - • Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
  - • Risk of serious infections
  - • The product should not be given to patients with active or suspected infection
  - • The product may lessen signs and symptoms of acute infection delaying the diagnosis
  - • Serious infusion reaction and their management
  - • Serious hypersensitivity reactions and their management

- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Reporting of serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Diagnosis of Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

Section 1. What RoActemra is used for of the PL

- **RoActemra is also used to treat patients 2 years of age and older** with active ***polyarticular juvenile idiopathic arthritis*** (***pJIA***), an inflammatory disease that causes pain and swelling in one or more joints. RoActemra is used to improve the symptoms of pJIA and can be given in combination with methotrexate or alone.

Section 2. What you need to know before you take RoActemra of the PL

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA ~~or~~ sJIA or pJIA.
Pregnancy, breast-feeding and fertility

RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant. Women of childbearing potential must use effective contraception during and up to 3 months after treatment.
Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

Available non-clinical data does not suggest an effect on fertility under tocilizumab treatment

Section 3. How RoActemra is given of the PL

Children with pJIA
The usual dose of RoActemra depends on your weight.
- If you weigh less than 30kg: the dose is 10mg per kg
- If you weigh 30kg or more: the dose is is 8 mg for every kilogram of body weight

The dose is calculated based on your body weight at each administration.

Children with pJIA will be given RoActemra once every 4 weeks through a drip in your vein (intravenous infusion) over one hour.

Section 4. Possible side effects of the PL

~~**SJIA Patients**~~
~~In general, the side effects in sJIA patients were similar in type to those seen in RA patients as stated above.~~

SJIA Patients
In general, the side effects in sJIA patients were similar in type to those seen in RA patients as stated above with the exception of nasopharyngitis, lower white blood cells, hepatic transaminases increased and diarrhea which were reported more frequently.

PJIA Patients
In general, the side effects in pJIA patients were similar in type to those seen in RA patients as stated above with the exception of nasopharyngitis, headache, nausea and lower white blood cells, which were reported more frequently,

Section 6. Contents of the pack and other information of the PL

Use in the paediatric population

SJIA and pJIA Patients ≥ 30 kg

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 100 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.4 ml/kg**) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

SJIA Patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.6 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

PJIA Patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.5 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

3. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

In the pivotal phase III study WA19977, the primary efficacy endpoint was the proportion of patients developing JIA ACR30 flare between Week 16 and Week 40. Patients receiving placebo and those receiving TCZ were compared. Three subsets of the JIA population were included in the study: RF-positive or RF negative pJIA, and extended oligoarticular arthritis.

The JIA ACR30 flares relative to week 16 in patients receiving TCZ was statistically significantly lower than the rate in patients receiving placebo (25.6% vs. 48.1%). The primary endpoint was met.

This result was supported by a predefined set of secondary analyses, controlling for multiple testing. To control for the type I error rate, the secondary endpoints were tested in a hierarchical fixed sequence approach. The chain of statistical significance in the hierarchical testing of secondary endpoints was broken after the seventh of 13 endpoints. The proportion of patients with JIA ARC/30/50/70 improvement was statistical significant higher in the TCZ group than in the placebo group. Change from baseline in number of active joints, in Physician's global assessments VAS and in pain VAS also demonstrated statistical significant superiority of TCZ over placebo.

Thus it can be considered that the results demonstrated a clinically relevant benefit in patients with RF-positive or RF negative pJIA, and extended oligoarticular arthritis.

Uncertainty in the knowledge about the beneficial effects

Impairment of growth is a common problem in juvenile rheumatoid arthritis (JRA), particularly in children with active disease. So far no data on the potential impact on TCZ therapy on growth retardation of in the paediatric population are available. Data on growth development are collected in part III of study WA19977 and will be provided with the final study report. The MAH should also

include monitoring the growth development in the paediatric registry as described in the risk management plan.

An increased prevalence of cardiovascular disease is documented in adult RA patients, it is suggested that chronic inflammation and impaired immune system are increasing the risk for atherosclerosis in this population. In paediatric patients there is also evidence that JIA is associated with increased risk for atherosclerosis, yet the data are scare. The MAH will collect post marketing data on the efficacy and safety of TCZ in children with pJIA in a paediatric registry as described in the risk management plan.

Risks

Unfavourable effects

The unfavourable effects of TCZ are established and include infection, allergic reactions including anaphylaxis, neutropenia, and thrombocytopenia, AST/ALT/bilirubin elevation and hypercholesterolaemia.

No new safety signals were identified. The safety profile of TCZ in paediatric population with pJIA is comparable with the safety profile in the adult RA population. The rates of adverse events, including SAEs, infections, serious infections and haematological abnormalities e.g. neutropenia and thrombocytopenia are lower than in the sJIA population.

Uncertainty in the knowledge about the unfavorable effects

The long term safety data of TCZ in the paediatric population is limited. The final report of the part III of study WA19977 is will provide further information. In addition, the MAH was requested to initiate a paediatric registry to generate long-term efficacy and safety data. This registry specifically addresses the occurrence/treatment of uveitis in pJIA patients as one patient experienced this event under treatment with TCZ. These measures are defined in the risk management plan and considered appropriate.

Benefit-risk balance

Importance of favourable and unfavourable effects

JIA is a major cause of disability in children. The prognosis depends on the adequacy of therapy. The aim the treatment is rapid suppression of inflammation in order to prevent organ damage, maximise physical function and promote normal growth and development.

The important clinical benefit of TCZ observed in the pivotal study WA19977 was a rapid alleviating of signs and symptoms in children with JRA in children which are unresponsive to MTX or who intolerant to MTX. The primary endpoint was met at the end of the placebo controlled withdrawal period at week 40. Furthermore, at the end of the active lead in period (week 16) clinically meaningful JIA ACR response rates (week 16) were achieved.

The safety profile of TCZ in the paediatric population with pJIA is comparable with the safety profile in the adult RA population. No new safety signals were identified. Appropriate risk minimisation measures (routine or additional) are included in the RMP.

Benefit-risk balance

The demonstrated clinical benefit of TCZ therapy in children with RF-positive or RF negative pJIA, and extended oligoarticular arthritis who are unresponsive or intolerant to MTX outweighs the risks. Appropriate risk minimisation measures (routine or additional) are included in the RMP. Additional long-term efficacy and safety data in pJIA will be provided with the final results of study WA19977 and information from a new paediatric registry, as described in the risk management plan. The benefit risk balance in the proposed indication and patient population is positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to extend the indication of tocilizumab to the treatment in combination with methotrexate (MTX) of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Sections 1, 2, 3, 4 and 6 of the Package Leaflet are updated accordingly. In addition, the MAH took the opportunity to include minor editorial changes throughout the PI.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA and sJIA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- The Summary of Product Characteristics
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
    - The product should not be given to patients with active or suspected infection
    - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Serious infusion reaction and their management
- Serious hypersensitivity reactions and their management
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Reporting of serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Diagnosis of Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and infusion reactions
- Preparation of infusion
- Infusion rate
- Monitoring of the patient for infusion reactions
- Reporting of serious adverse drug reactions

The Patient Information Pack should contain the following key elements:

- Patient Information Leaflet

- Patient Alert Card
    - to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.
    - to address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/277/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC).

5. EPAR changes

The EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to extend the indication of tocilizumab to the treatment in combination with methotrexate (MTX) of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Sections 1, 2, 3, 4 and 6 of the Package Leaflet are updated accordingly. In addition, the MAH took the opportunity to include minor editorial changes throughout the PI.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Summary

Please refer to the Scientific Discussion RoActemra/H/C/00955/II/26 for further information.