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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0097

Note

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



Status of this report and steps taken for the assessment				
Current step	Description	Planned date	Actual Date	Need for discussion
<input type="checkbox"/>	Start of procedure	25 May 2020	25 May 2020	<input type="checkbox"/>
<input type="checkbox"/>	CHMP Rapporteur Assessment Report	23 Jun 2020	23 Jun 2020	<input type="checkbox"/>
<input type="checkbox"/>	PRAC Rapporteur Assessment Report	26 Jun 2020	26 Jun 2020	<input type="checkbox"/>
<input type="checkbox"/>	PRAC members comments	01 Jul 2020	n/a	<input type="checkbox"/>
<input type="checkbox"/>	Updated PRAC Rapporteur Assessment Report	02 Jul 2020	n/a	<input type="checkbox"/>
<input type="checkbox"/>	PRAC endorsed relevant sections of the assessment report	09 Jul 2020	09 Jul 2020	<input type="checkbox"/>
<input type="checkbox"/>	CHMP members comments	13 Jul 2020	n/a	<input type="checkbox"/>
<input type="checkbox"/>	Updated CHMP Rapporteur Assessment Report	16 Jul 2020	n/a	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Opinion	23 Jul 2020	23 Jul 2020	<input type="checkbox"/>

Table of contents

1. Background information on the procedure	4
2. Overall conclusion and impact on the benefit/risk balance	4
3. Recommendations	6
4. EPAR changes	6
5. Introduction	8
6. Clinical Pharmacology aspects	8
6.1. Methods – analysis of data submitted	9
6.2. Results	10
6.3. Discussion.....	13
7. Clinical Efficacy aspects	14
7.1. Methods – analysis of data submitted	14
7.2. Results	17
7.3. Discussion.....	23
8. Clinical Safety aspects	24
8.1. Methods – analysis of data submitted	24
8.2. Results	24
8.3. Discussion.....	31
8.4. Direct Healthcare Professional Communication.....	32
9. Risk management plan	32
9.1. Overall conclusion on the RMP	35
10. Changes to the Product Information	35
11. Attachments	36

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 12 May 2020 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 4.2 of the SmPC for RoActemra 20 mg/mL concentrate for solution for infusion in order to amend the existing recommendations for monitoring of laboratory abnormalities in systemic juvenile idiopathic arthritis (sJIA) patients based on final results from study WA28029 (ARTHUR) listed as a category 3 study in the RMP; this is a Phase IV study to evaluate decreased dose frequency in sJIA who experience laboratory abnormalities during treatment with tocilizumab. The submission of the final study report for study WA28029 (ARTHUR) fulfils requirements of Article 46 of the paediatric regulation. The RMP version 26.0 has also been submitted. Changes to the RMP reflect the completion of study WA29029 (ARTHUR) and study WA22480 (ARTIS) which was assessed as part of variation EMEA/H/C/000955/II/0094.

The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

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

RoActemra (tocilizumab, TCZ) treatment is associated with certain laboratory abnormalities, including thrombocytopenia, neutropenia, and liver enzyme abnormalities. Recommendations in the SmPC for the sJIA patients are to stop TCZ dosing until the laboratory abnormality resolves.

At the time of opinion for TCZ in the treatment of sJIA in 2011, there was a post approval measure (PAM) to investigate the possibility of dose reduction in response to predefined laboratory abnormalities in sJIA patients.

Study WA28029 (ARTHUR) is a 96-week, two part, Phase IV study to explore the efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of intravenous TCZ in reduced dosing frequency regimens in patients with adequately controlled sJIA who had experienced a pre-defined laboratory abnormality which had resolved on TCZ twice weekly dosing.

The purpose of Study WA28029 (ARTHUR) was to investigate the use of less frequent dosing upon reinitiating treatment in patients who have achieved a high level of efficacy with TCZ but have experienced these laboratory abnormalities. It was conducted in fulfilment of the PAM.

The study comprised a run-in phase (Part 1) and the main study (Part 2). Patients could enter Part 2 directly, or via Part 1.

The objective of Part 1 was to increase enrolment into Part 2 by identifying patients with resolved laboratory abnormalities in Part 1 on the TCZ every two weeks (Q2W) regimen who would be eligible to participate in Part 2.

The objective of Part 2 was to assess the efficacy, safety, pharmacodynamics, pharmacokinetics, and patient reported outcomes of TCZ in reduced dosing frequency regimens.

The approved intravenous (IV) formulation of tocilizumab (TCZ) 20 mg/ml concentrate for solution for infusion in 10 ml vials was used as test product in the study. Patients received TCZ according the approved posology.

Pharmacokinetics and Population PK

Reduction of the dosing frequency from Q2W to Q3W and Q2W to Q4W led to a decrease in exposure metrics. Post-infusion concentration (C_{max}) at 12 weeks decreased due to a lower accumulation, with -16 and -26% from Q2W to Q3W and Q2W to Q4W, respectively. The area under the curve during a dosing interval (AUC_t) is decreasing in the same proportion with -15 and -30%, respectively. The decrease of the concentration at the end of a dosing interval (C_{min}) was observed to be more pronounced with -64 and -87% from Q2W to Q3W and Q2W to Q4W, respectively, and can be contributed to target mediated drug disposition (TMDD).

The decrease in exposure, especially in C_{min}, was not indicated to have major impact on response in terms of IL-6, sIL-6R levels and PD parameters.

Although the sample size is rather low (N=22; 495 measurable serum concentrations), PK results indicate that the PK concentration-time data for sJIA patients following decreased dose frequency were consistent with the previously established pharmacokinetic characteristics and population PK model developed for tocilizumab in sJIA patients. PK parameter C_{min} at week 12 changed the most with extension of dosing interval. Compared to Q2W, when the dosing interval increased to Q3W and Q4W, the mean C_{min} decreased from 74.7 µg/mL to 27.2 µg/mL and 9.73 µg/mL, respectively. C_{max} and AUC_t decreased with about 15% (Q3W) and 30% (Q4W).

As PK is characterized by a high degree of TMDD and by a strong effect of body weight on PK, conclusions on the PK/PD relationship with respect to efficacy and safety in general should be drawn with caution, given the small population Part 2 of the study is based on.

Efficacy Results

Nineteen 19 patients enrolled in Part 1, and finally 22 patients were enrolled into Part 2; 16 patients enrolled directly into Part 2, and an additional 6 patients entered via Part 1. Of these 22 patients, 7 patients completed the study under the in Part 2 of the study is rather small.

The key efficacy measures were Juvenile Arthritis Disease, Juvenile Idiopathic Arthritis (JIA) flare, and fever (attributable to sJIA).

JADAS-71 scores generally remained near the level of inactive disease (<1.0) for the majority of patients throughout the study during TCZ IV Q3W and TCZ IV Q4W dosing. There were increases in the JADAS-71 scores at the time of sJIA flare as expected.

Overall, sJIA continued to be well-controlled (no flare) in 17/22 patients (77%) during Part 2. Five patients (23%) experienced a flare during the study with one patient experiencing two flares (at consecutive study visits).

During TCZ IV Q3W dosing, three of the 15 patients on 8 mg/kg TCZ flared, and one of the seven patients on 12 mg/kg TCZ flared. The flares occurred at Week 9, Week 12, Week 15 (8 weeks after last dose of study drug), and in one patient at Week 18 and 21. One of the seven patients who transitioned to TCZ IV Q4W flared during Q4W dosing at Week 32 (week 53 from Part 2 baseline). The patient was receiving TCZ IV 8 mg/kg.

There were no patients who experienced fever due to sJIA during the study.

In conclusion, the data indicated that sJIA continued to be well-controlled during the reduced dosing frequency regimens of TCZ IV Q3W and Q4W. However, the CHMP noted that the data base is rather small, which precluded a robust conclusion.

Safety results

The safety outcomes from this study were similar to those achieved in other studies with TCZ IV Q2W and were consistent with the known safety profile of TCZ IV in sJIA. No new or unexpected safety concerns were observed.

In conclusion, the study showed that sJIA patients who had experienced a laboratory abnormality (low neutrophils, low platelets, or increased ALT or AST) during IV TCZ Q2W treatment could maintain efficacy during an increased dosing interval of TCZ IV Q3W or Q4W. However, the data are not considered sufficient to introduce a dose adjustment in sJIA patients who experience laboratory abnormalities. Therefore, Section 4.2 of the SmPC is revised as follows:

“There are insufficient clinical data to assess the impact of a tocilizumab dose reduction in sJIA patients who have experienced laboratory abnormalities.”

The benefit-risk balance of RoActemra, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 4.2 of the SmPC for RoActemra 20 mg/mL concentrate for solution for infusion in order to amend the existing recommendations for monitoring of laboratory abnormalities in systemic juvenile idiopathic arthritis (sJIA) patients based on final results from study WA28029 (ARTHUR) listed as a category 3 study in the RMP; this is a Phase IV study to evaluate decreased dose frequency in sJIA who experience laboratory abnormalities during treatment with tocilizumab. The submission of the final study report for study WA28029 (ARTHUR) fulfils requirements of Article 46 of the paediatric regulation. The RMP is updated to version 26.0 to reflect the completion of study WA29029 (ARTHUR) and study WA22480 (ARTIS) which was assessed as part of variation EMEA/H/C/000955/II/0094.

is recommended for approval.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion RoActemra EMEA/H/C/000955/II/0097.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

TCZ treatment is associated with certain laboratory abnormalities, including thrombocytopenia, neutropenia, and liver enzyme abnormalities. Dose modification recommendations in sJIA are to stop TCZ dosing until the laboratory abnormality resolves.

The EMA approval of TCZ for the treatment of sJIA in 2011 was on condition that a post approval measure (PAM) be completed. This PAM was to investigate the possibility of dose reduction in response to predefined laboratory abnormalities in sJIA patients.

Study WA28029 (ARTHUR) was a 96-week, two part, Phase IV study to explore the efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of intravenous tocilizumab (TCZ) in reduced dosing frequency regimens in patients with adequately controlled sJIA who had experienced a pre-defined laboratory abnormality which had resolved on TCZ twice weekly dosing.

The purpose of Study WA28029 (ARTHUR) was to investigate the use of less frequent dosing upon reinitiating treatment in patients who have achieved a high level of efficacy with TCZ but have experienced these laboratory abnormalities

The study comprised a run-in phase (Part 1) and the main study (Part 2). Patients could enter Part 2 directly, or via Part 1.

The objective of Part 1 was to increase enrolment into Part 2 by identifying patients with resolved laboratory abnormalities in Part 1 on the TCZ every two weeks (Q2W) regimen who would be eligible to participate in Part 2.

The objective of Part 2 was to assess the efficacy, safety, pharmacodynamics, pharmacokinetics, and patient reported outcomes of TCZ in reduced dosing frequency regimens.

The approved intravenous (IV) formulation of tocilizumab (TCZ) 20 mg/ml concentrate for solution for infusion in 10 ml vials was used as test product in the study.

6. Clinical Pharmacology aspects

STUDY WA28029

The objective of Part 2 was to assess the efficacy, safety, pharmacodynamics, pharmacokinetics, and patient reported outcomes of tocilizumab in reduced dosing frequency regimens.

The PK objective in Part 2 of the study was to describe the pharmacokinetics of tocilizumab in reduced dosing frequency regimens. The primary PD objective in Part 2 of the study was to describe the pharmacodynamics using sIL-6R and C-reactive protein (CRP), and immunogenicity of tocilizumab in reduced dosing frequency regimens.

Please see Efficacy section for Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP); Interleukin-6, and Interleukin-6 Soluble Receptor (sIL-6R).

In the WA28029 study, doses of 8 mg/kg for patients ≥ 30 kg and 12 mg/kg for patients < 30 kg were used, as per the approved global TCZ sJIA label. Dose selection adjustment in Part 2 of Q3W and Q4W was designed in conjunction with the EMA to address the post approval measure to investigate the dose reduction response to predefined laboratory abnormalities in sJIA patients.

Once patients entered Part 2 they received tocilizumab dosed by body weight (12 mg/kg for patients <30kg; 8 mg/kg for patients ≥ 30 kg) by IV infusion every three weeks (Q3W) for a minimum of 5 consecutive infusions. Each patient maintained Q3W dosing of TCZ in the study up to 52 weeks unless the patient experienced a predefined laboratory abnormality. Following the occurrence and resolution of the laboratory abnormality, patients who maintained adequate disease control (JADAS ≤ 3.8 and absence of fever attributable to sJIA) moved to dosing every 4 weeks (Q4W) of tocilizumab.

6.1. Methods – analysis of data submitted

Bioanalytics

Determination of the serum concentration of TCZ was conducted using ELISA, with the limit of quantification (LOQ) was 100 ng/mL. The assay precision (CV%) ranged from 9.9% to 14.5%. The overall accuracy (% relative error) ranged from 95.5% to 103.9%.

PK and PD data

The study screened 20 patients in Part 1, of which 19 patients enrolled to receive TCZ IV Q2W. A total of 26 patients were screened for entry into Part 2 (which included patients who had previously participated in Part 1, and patients who were entering Part 2 directly). Of these 26 patients, 22 were enrolled into Part 2; 16 patients enrolled directly into Part 2, and an additional 6 entered via Part 1.

All patients had sparse serum PK samples taken.

For Q3W regimen, the following PK samples were collected:

- Pre-dose at baseline and at weeks 3, 6, 9, 12, 24, 36, and 48.
- Post-dose (obtained within 15 minutes following end of infusion): day 1 and weeks 3, 6 and 9.
- At any time point during the day at weeks 1, 2, 10 and 11.

For Q4W regimen, the following PK samples were collected:

- Pre-dose at baseline and at weeks 4, 8 and 12.
- Post-dose (obtained within 15 minutes following end of infusion): day 1 and week 4 and 8
- At any time point during the day at weeks 1, 2, 3, 9, 10 and 11

For patients who withdrew from the study a PK sample was taken 2 weeks after last study drug.

Safety, safety laboratory, PK, PD, and efficacy assessments were performed during Part 2 of the study as described in the schedule of assessments.

PK Analysis

A detailed analysis of the PK data using population PK modelling was performed. The PK model developed for sJIA patients from previous studies (WA28118 and WA18221) using IV and SC data was used to analyze the serum concentration-time data. Nonlinear mixed effects modelling (using NONMEM software) was used to analyze the serum concentration-time data collected in Part 2 of the study. A Bayesian feedback analysis was conducted by fixing the TCZ population PK parameters and by assuming that PK properties of tocilizumab are consistent in sJIA patients across the different dosing frequencies.

The following systemic exposure parameters were estimated for all patients who provided adequate PK samples:

- AUC τ during a dosing interval at week 12 of Part 2; $\tau = 3$ weeks for Q3W and $\tau = 4$ weeks for Q4W

- C_{max} post infusion at Week 12 of Part 2 of the study
- C_{min} at end of a dosing interval at Week 12 of Part 2 of the study

TCZ serum concentrations and computed PK parameters are listed and summarized descriptively. Mean and median serum concentrations versus time are plotted on linear scales. Patient data were included in the PK analysis if it contained sufficient dosing information and at least one adequately documented and quantifiable TCZ concentration per patient.

TCZ serum concentrations and serum concentration of PD markers are summarized descriptively by dose frequency and body weight dosing category. Mean (\pm standard error of mean) or median (with interquartile range) serum concentrations versus time are presented graphically.

TCZ serum concentration response relationship (PD markers and efficacy parameters) were also explored. TCZ serum concentration individual profiles were presented with JADAS-71 individual results at visits, together with the eventual presence of JIA flare and fever attributable to sJIA.

Immunogenicity

Samples for anti-TCZ antibodies were collected for all patients to evaluate the immunogenicity of tocilizumab at baseline and Week 24 for patients on Q2W in Part 1. In addition, samples were collected at baseline, Week 6, 12, 24, 36, and 48 (for patients on Q3W dosing in Part 2) and at baseline, eight weeks, and 12 weeks after switching to Q4W for patients on Q4W dosing in Part 2 of the study. Samples were collected at the last study visit, or at the time of early withdrawal from the study (visit WD1) for Part 1 or Part 2 of the study. Event-driven sampling (at the time of the event and at least 6 weeks after the last dose) occurred for all patients experiencing serious infusion-related or allergic reactions or any hypersensitivity event (including non-serious events) leading to treatment withdrawal in Part 1 or Part 2 of the study.

Blood samples were collected from all patients for the evaluation of immunogenicity of tocilizumab using a "tiered" testing strategy by immunogenicity assays:

- All samples were tested with a screening assay, and those samples that were positive were further analyzed with a confirmation assay to confirm specificity
- If the confirmation assay was positive, an additional two tests were performed to characterize the detected ADA; a neutralizing assay was to test ADA's neutralizing potential, and an IgE assay was to verify whether the detected ADA were of the IgE isotype

Based on the testing strategy, if the screening assay of a given serum sample was negative, then the results of the confirmation, neutralizing and IgE assays were assumed to be negative. If the screening assay was positive, and the confirmation assay was negative, then the results of neutralizing assay and IgE assay were assumed to be negative.

Since only one patient at baseline in Part 1 and no patients in Part 2 of the study presented with positive antibodies only a listing was produced.

6.2. Results

Population PK analyses of tocilizumab following IV and SC administration in sJIA patients 1-17 years old were previously conducted using a PK database composed of 878 PK samples from 89 patients from the Phase 3 Study WA18221 (IV administration) and 832 PK samples from 51 patients from the Phase 1b Study WA28118 (SC administration). The population model that best described the serum concentration-time profiles of TCZ was a two-compartment open model with parallel linear and Michaelis-Menten eliminations.

This tocilizumab population model was used as reference to analyze the PK data collected in Part 2 of the Study WA28029 in sJIA patients with decreased dose frequency.

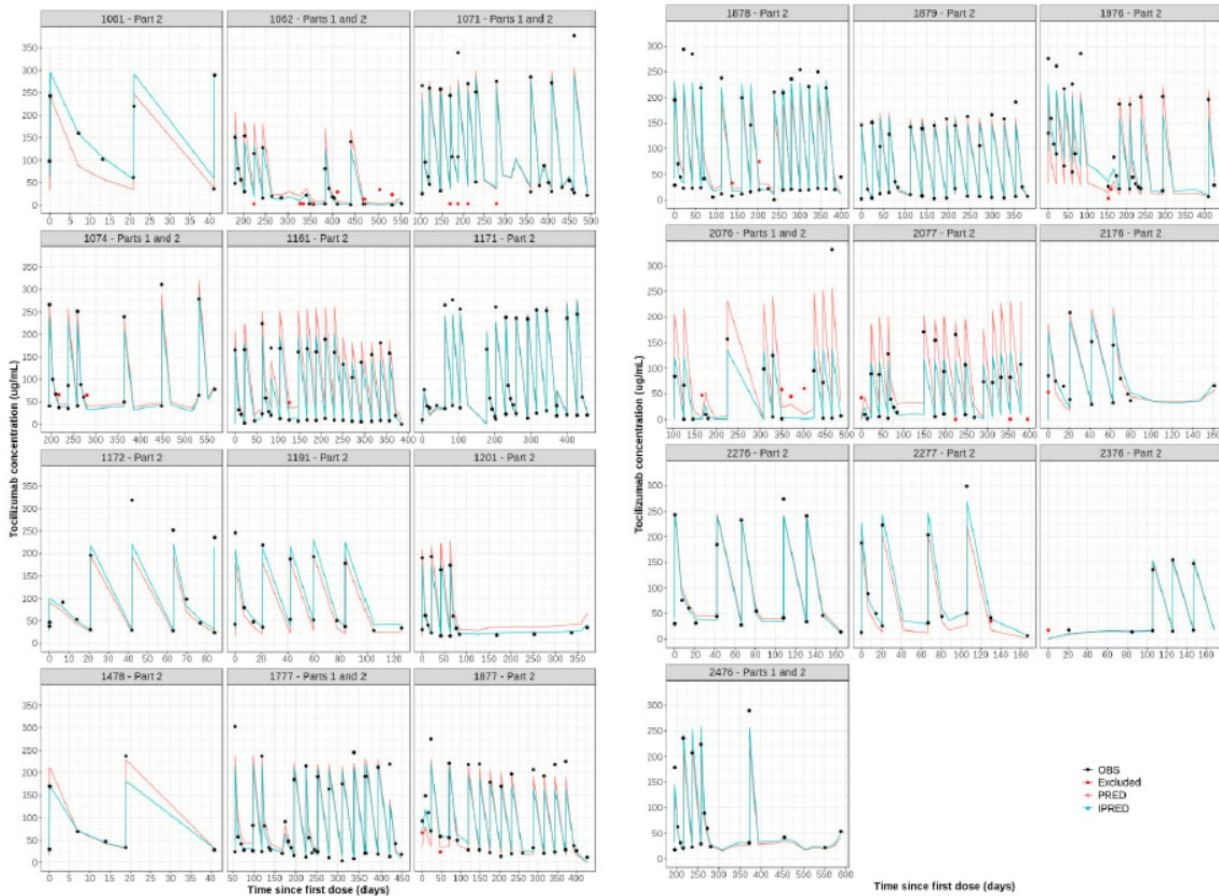
In total, 577 tocilizumab serum concentrations measured from 22 sJIA patients who entered Part 2 in Study WA28029 were available for the pop PK analyses. During tocilizumab treatment, 5.5% (n=32) of the serum concentrations from 7 sJIA patients were BLQ and were excluded from the analysis dataset.

Dosing information was missing in 7 patients who continued to receive tocilizumab after the end of the Part 2. The serum concentrations for tocilizumab collected following those administrations were excluded from the analysis dataset. They represented 2.3% (n=13) of the serum concentrations.

In addition, 5.7% (n=33) of the serum concentrations were excluded from the dataset due to their inconsistent serum concentration levels. Fifteen of those inconsistent serum concentrations were selected to be re-assayed. Finally, only 4 concentrations from the same patient could be re-assayed and the new concentrations were very similar to the previous concentrations.

The final PK dataset was composed of 22 patients from Phase IV Study WA28029, with a total of 495 measurable TCZ serum concentrations following the 8 mg/kg IV for sJIA patients weighing ≥ 30 kg and 12 mg/kg IV Q2W for sJIA patients weighing < 30 kg, either Q3W or Q4W. Patients in Study WA28029 ranged from 5 to 17 years old, with the median age of 10 years. A majority of patients in both Part 1 (89.5%) and Part 2 (81.8%) were of white ethnicity. By gender 52.6% (10 patients) were male and 47.4% (9 patients) were female patients ranging in age from 3 to 17 years of age in Part 1. In Part 2, 63.4% (14 patients) of patients enrolled were female and 36.4% (8 patients) were male ranging in age from 5 to 17 years of age. Median weight was 32.5 kg in Part 1 and 38.5 kg in Part 2. Ten of the 19 patients enrolled in Part 1 had previously received tocilizumab, and 9 were tocilizumab -naive. As it was a prerequisite for study entry, all patients entering Part 2 had previously received tocilizumab, and were in clinical remission of sJIA at baseline. Only one patient at baseline in Part 1 and no patients in Part 2 of the study developed anti-drug antibodies.

Evaluation of the results from the Bayesian feedback analysis showed that the PK concentration-time data for sJIA patients with decreased tocilizumab dose frequency are in full agreement with the population PK model previously developed for tocilizumab. The individual fits for the serum concentration-time profiles showed that the population PK model previously developed for sJIA patients was able to describe the PK concentration data for sJIA patients with decreased dosing frequency. The serum concentrations that were removed due to inconsistencies are indicated in red in those individual plots of individual serum concentration -time courses which are depicted below (linear scale).



Source: Appendix 4, p. 1574-1575 of CSR.

To show the changes induced by the reduction of the dosing frequency from Q2W to Q3W and Q2W to Q4W, on the secondary PK parameters, simulations were conducted using the individual primary PK parameters of the 22 sJIA patients.

As expected, the increase of the dosing interval led to a decrease of the post-infusion concentration (C_{max}) at 12 weeks due to a lower accumulation, with -16% and -26% from Q2W to Q3W and Q2W to Q4W dosing, respectively. The area under the curve during a dosing interval (AUC_T) decreased in the same proportion with -15% and -30%, respectively. The decrease of the concentration at the end of a dosing interval (C_{min}) was more pronounced with -64% and -87% from Q2W to Q3W and Q2W to Q4W dosing, respectively (see table below). The larger decrease in C_{min} was due to the concentration dependent clearance of tocilizumab that represents the target mediated drug disposition (TMDD). The longer the dosing interval is for a given dose, the more important will be the contribution of TMDD and in turn, more pronounced will be the decrease of C_{min} .

The analysis of PK parameters (C_{max} , C_{min} , AUC) demonstrated tocilizumab serum concentrations were consistent with other sJIA tocilizumab studies in patients 2-17 years of age.

Compared to Q2W, when the dosing interval increased to Q3W and Q4W, the mean C_{min} decreased from 74.7 µg/mL to 27.2 µg/mL and 9.73 µg/mL, respectively. The concentration post infusion (C_{max}) also decreased but with lower magnitude from 253 µg/mL to 213 µg/mL and 187 µg/mL, respectively. Similarly, the area under the curve (AUC_T) during a dosing interval at week 12, decreased from 1785 µg/mL to 1516 µg/mL and 1245 µg/mL × day, respectively.

Table 1 Simulated Secondary PK Parameters at Week 12 Following 8 mg/kg IV for sJIA Patients Weighing ≥ 30 kg and 12 mg/kg IV for sJIA patients Weighing < 30 kg Q2W, Q3W or Q4W

Steady-State Parameter	<u>Q2W</u>	<u>Q3W</u>	<u>Q4W</u>
	Mean (SD)	Mean (SD)	Mean (SD)
	Median (Min/Max) n = 22	Median (Min/Max) n = 22	Median (Min/Max) n = 22
C_{min} at week 12 ($\mu\text{g/mL}$)	74.7 (31.7) 75.9 (27.3/146)	27.7 (15.6) 23.5 (7.60/65.4)	9.73 (7.80) 8.32 (0.693/32.2)
C_{max} at week 12 ($\mu\text{g/mL}$)	253 (56.5) 261 (126/335)	213 (53.3) 207 (116/311)	187 (51.3) 180 (104/298)
AUC_T at week 12 ($\mu\text{g/mL} \times \text{day}$)	1785 (557) 1839 (836/2903)	1516 (460) 1434 (826/2556)	1245 (375) 1298 (662/2190)

A by patient listing of the PK results ([1_pk_PK_P2](#)) in Part 2 of the study is appended.

Source: CRS, p.80.

6.3. Discussion

Study WA28029 (ARTHUR) was a 52-week study (Part 2), following a run-in phase (Part 1) of 24 weeks. Part 2 of the study aimed at exploring the clinical pharmacology in terms of PK, PD and immunogenicity of IV TCZ in a reduced dosing frequency in patients who had adequately controlled sJIA and experienced a pre-defined laboratory abnormality that had resolved on TCZ twice weekly dosing.

In the main study (Part 2) patients received TCZ IV Q3W or Q4W dosing (8 mg/kg or 12 mg/kg depending on body weight with body weight cut of 30 kg).

Overall, the study had a small sample size with 22 patients enrolled in Part 2 of the study.

Pharmacokinetics and Pop PK

The serum concentration-time courses for TCZ in sJIA patients with decreased TCZ dose frequency were consistent with the previously established pharmacokinetic characteristics and pop PK of TCZ in sJIA patients.

This previously established population PK model was used as reference to analyze the PK data collected in Part 2 of the Study WA28029 in sJIA patients with decreased tocilizumab dose frequency. The model is deemed fit for that purpose. A Bayesian feedback analysis was conducted by fixing the tocilizumab population PK parameters and by assuming that PK properties are consistent in sJIA patients across the different dosing frequencies.

The final PK dataset resulting from Phase IV Study WA28029 consisted of 495 measurable serum concentrations following the 8 mg/kg IV for sJIA patients weighing ≥ 30 kg and 12 mg/kg IV Q2W for sJIA patients weighing < 30 kg, either Q3W or Q4W. Patients in Study WA28029 ranged from 5 to 17 years old, with the median age of 10 years.

Evaluation of PK results indicate that the PK concentration-time data for sJIA patients with decreased TCZ dose frequency are in agreement with the population PK model previously developed for TCZ.

Reduction of the dosing frequency from Q2W to Q3W and Q2W to Q4W led to a decrease in exposure metrics. Post-infusion concentration (C_{max}) at 12 weeks decreased due to a lower accumulation, with -16

and -26% from Q2W to Q3W and Q2W to Q4W, respectively. The area under the curve during a dosing interval (AUC_t) is decreasing in the same proportion with -15 and -30%, respectively. The decrease of the concentration at the end of a dosing interval (C_{min}) was observed to be more pronounced with -64 and -87% from Q2W to Q3W and Q2W to Q4W, respectively, and can be contributed to target mediated drug disposition (TMDD).

PK/PD

The decrease in exposure, especially in C_{min}, was not indicated to have major impact on response in terms of IL-6, sIL-6R levels and PD parameters (please compare Section Efficacy).

In conclusion, although the sample size is rather low (N=22; 495 measurable serum concentrations) PK results indicate that PK following decreased dose frequency were consistent with the previously established pharmacokinetic characteristics and pop PK of tocilizumab in sJIA patients. PK parameter C_{min} at week 12 changed the most with extension of dosing interval. Compared to Q2W, when the dosing interval increased to Q3W and Q4W, the mean C_{min} decreased from 74.7 µg/mL to 27.2 µg/mL and 9.73 µg/mL, respectively. C_{max} and AUC_t decreased with about 15% (Q3W) and 30% (Q4W).

As PK is characterized by a high degree of TMDD and by a strong effect of body weight on PK, conclusions on the PK/PD relationship with respect to efficacy and safety in general should be drawn with caution, given the small population Part 2 of the study is based on.

7. Clinical Efficacy aspects

Study WA28029 (ARTHUR)

Study WA28029 (ARTHUR) was a 96-week, two part, Phase IV study to explore the efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of intravenous tocilizumab (TCZ) in reduced dosing frequency regimens in patients with adequately controlled sJIA who had experienced a pre-defined laboratory abnormality which had resolved on TCZ twice weekly dosing.

The purpose of Study WA28029 (ARTHUR) was to investigate the use of less frequent dosing upon reinitiating treatment in patients who have achieved a high level of efficacy with TCZ but have experienced these laboratory abnormalities

The study comprised a run-in phase (Part 1) and the main study (Part 2). Patients could enter Part 2 directly, or via Part 1.

7.1. Methods – analysis of data submitted

• Study participants

Part 1: sJIA patients who were TCZ naïve with an inadequate clinical response to NSAIDs or corticosteroids, or TCZ non-naïve patients.

Part 2: Patients with adequately controlled sJIA (JADAS Minimal Disease Activity score of 3.8 or less and absence of fever [due to sJIA] at screening and baseline for Part 2) who experienced a laboratory abnormality which had resolved at any time on TCZ twice weekly dosing. Patients could enter Part 2 directly without participating in Part 1, or via Part 1.

Key inclusion criteria

Part 1 and 2:

- Age 2 years up to and including 17 years at screening into trial.

- sJIA according to International League of Associations for Rheumatology (ILAR) classification (2001).
- sJIA symptoms that lasted for at least 1 month since diagnosis of sJIA.
- Not receiving methotrexate (MTX) or discontinued MTX at least 4 weeks prior to the Part 1 or Part 2 baseline visit, or was taking MTX for at least 12 weeks immediately prior to the Part 1 or Part 2 baseline visit and on a stable dose of ≤ 20 mg/m² for at least 8 weeks prior to the Part 1 or Part 2 baseline visit, together with either folic acid or folinic acid according to local standard of care.

Part 2

- JADAS-71 score of 3.8 or less and absence of fever (related to sJIA) at screening and baseline of Part 2
- Neutropenia, thrombocytopenia, or elevated ALT/AST (as per criteria in protocol) previously experienced (and resolved) on the labelled dose (Q2W) of TCZ.

Table 2: Laboratory Abnormalities Serving as Inclusion Criteria for Part 2 of the Study When Experienced (with Resolution) on Q2W TCZ

Abnormality	Results Range
Neutropenia	ANC 0.5 to 1.0 x 10 ⁹ /L
Thrombocytopenia	Platelets 50 to 100 x 10 ⁹ /L
Elevated liver enzymes	ALT/AST >1 to 3 x ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal.

Source: CSR p 32

- Not currently receiving oral corticosteroids, or taking oral corticosteroids at a stable dose for a minimum of 2 weeks prior to the Part 2 baseline visit at no more than 10 mg/day or 0.2 mg/kg/day, whichever is less.
- Not taking non-steroidal anti-inflammatory drugs (NSAIDs), or taking no more than 1 type of NSAID at a stable dose for a minimum of 2 weeks prior to the Part 2 baseline visit, with the dose being less than or equal to the maximum recommended daily dose.

- **Treatments**

Part 1: TCZ 12 mg/kg for patients < 30 kg; 8 mg/kg for patients \geq 30 kg by IV infusion every 2 weeks (Q2W) for up to 24 weeks or until the patient experienced an event of neutropenia, thrombocytopenia, or liver enzyme abnormality according to the protocol.

Part 2: TCZ 12 mg/kg for patients < 30 kg; 8 mg/kg for patients \geq 30 kg by IV infusion Q3W for up to 52 weeks, unless they experienced a pre-defined laboratory abnormality. Following the occurrence and resolution of a pre-defined laboratory abnormality, patients who had maintained adequate disease control, and had received a minimum of 5 consecutive Q3W infusions in Part 2 of the study, were moved to Q4W dosing of TCZ.

- **Objectives**

Part 1:

The objective of Part 1 was to increase enrolment into Part 2 by identifying patients with resolved laboratory abnormalities in Part 1 on the TCZ every two weeks (Q2W) regimen who would be eligible to participate in Part 2.

Part 2:

- To explore the efficacy of tocilizumab (TCZ) in reduced dosing frequency regimens (every 3 weeks (Q3W) and every four weeks (Q4W), as appropriate) using the Juvenile Arthritis Disease Activity Score (JADAS)-71, JIA flare, and fever (attributable to sJIA)
- To evaluate the safety of TCZ in reduced dosing frequency regimens
- To describe the pharmacodynamics using interleukin-6 soluble receptor (IL-6 sR), C-reactive protein (CRP), and immunogenicity of TCZ in reduced dosing frequency regimens (see above)
- To describe the pharmacokinetics of TCZ in reduced dosing frequency regimens (see above)
- To describe the Child Health Assessment Questionnaire (CHAQ) outcomes (consisting of three components: Disability Index, Parent's/Patient's Global Assessment of Overall Well-Being, and Parental/Patient Pain Index) with TCZ in reduced dosing frequency regimens

- **Outcome/endpoints**

Assessment of JADAS-71, JIA flare and fever attributable to sJIA in Part 2 of the study. Patient reported outcomes (PRO) using the CHAQ.

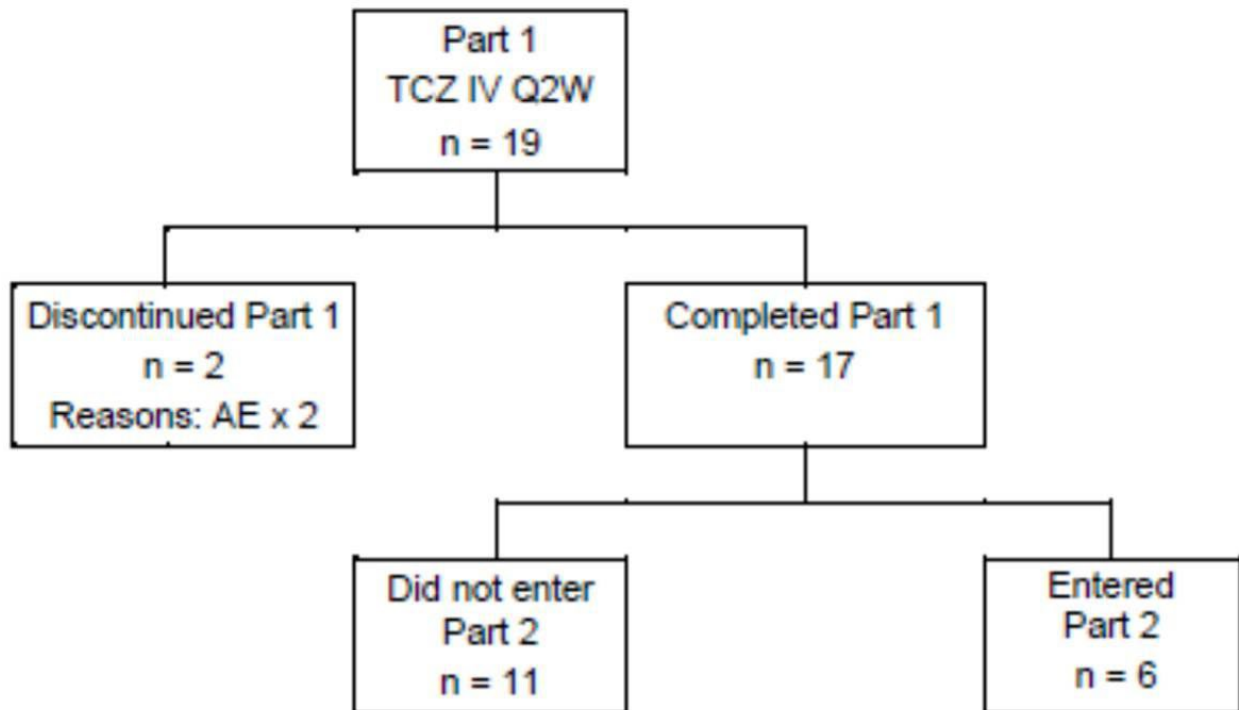
- **Statistical methods**

No hypothesis testing was performed. Data is presented descriptively (e.g., mean, median, minimum, and maximum for quantitative variables).

7.2. Results

- Participant flow

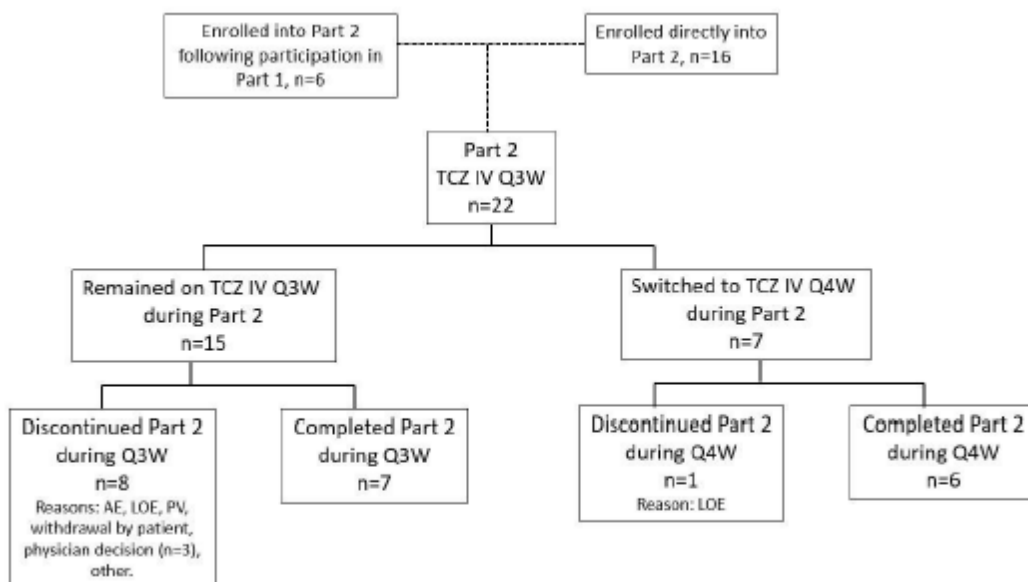
Figure E1: Patient Disposition in Part 1 of the Study



Source: CSR p 55

In total, two patients discontinued from Part 1 of the study, both due to AEs.

Figure E2: Patient Disposition in Part 2 of the Study



AE = adverse event; LOE = lack of efficacy; IV = intravenous; PV = protocol violation; Q3W = every three weeks; Q4W = every four weeks; TCZ = tocilizumab

Source: CSR p 56

In Part 2 of the study, eight patients (36.4%) receiving TCZ Q3W were discontinued from the study. For the patients on TCZ Q3W at the time of withdrawal, three patients discontinued due to physician decision, and one patient each for lack of efficacy, protocol violation (violation of entry criteria), AE, withdrawal by the patient, and 'other'. Two of the patients who were withdrawn due to physician decision were in clinical remission of their sJIA, and a reduced TCZ dosing regimen was sought outside of the protocol, and one patient was withdrawn by the physician due to needle phobia. The patient who withdrew due to 'other' reason actually withdrew due to a flare of their sJIA.

One patient receiving TCZ Q4W withdrew from the study due to lack of efficacy.

During Part 2 of the study, only one patient switched TCZ dosing based on body weight. This patient switched from 12 mg/kg to 8 mg/kg during Q3W dosing. For reporting purposes, the weight-dosing category observed at baseline for this patient was considered constant during the whole of Part 2. No patients switched dosing regimen due to a change in body weight in Part 1.

- **Conduct of the study**

Part 1

There were six protocol deviations in four patients. The deviations were for overdosage of study drug (4 deviations in two patients), violation of exclusion criteria (medical history), and violation of laboratory criteria. The patient who experienced a protocol deviation for violation of laboratory criteria continued to Part 2 of the study.

Part 2

There were seven protocol deviations in six patients. One patient had a violation of the inclusion criteria and a violation relating to medication (NSAID dose not stable prior to study entry). Three patients had deviations for medications; one patient received commercial TCZ instead of study medication, one patient received incorrect TCZ doses due to a change in body weight, and in one patient the NSAID dose was not stable during the first 12 weeks of Part 2. The other patients had deviations of the exclusion criteria (prohibited medical history - duodenal ulcer perforation), and inclusion criteria (signed ICF).

No deviations led to the exclusion of data from the analysis.

- **Baseline data**

Part 1 (safety population)

There were nine females and 10 males, the majority of them were white (17/19: 89.5%), and of non-hispanic or latino ethnicity (13/19: 68.4%). Thirteen patients (68.4%) were between 2 and <11 years of age and six patients (31.6%) were aged 11 to <18 years. Median weight was 32.5 kg. The median disease duration from the date of first diagnosis was 0.7 (range 0.1 – 15.2) years. A total of 9/19 patients (47.4%) reported previous non-biologic DMARD use, and 12/19 patients (63.2%) had previous biologic DMARD use (including previous use of TCZ) (Table 6). Patients could have received treatment with TCZ prior to entry into Part 1 or be TCZ-naïve at Part 1 entry; 10 of the 19 patients enrolled in Part 1 had previously received TCZ.

Part 2

In Part 2 of the study, there were 22 patients (8 male and 14 female) with 11/22 patients (50%) between 2 to <11 years of age and 11/22 patients (50%) between 11 to < 18 years of age. Most of the patients were white (18/22: 81.8%) and of non-hispanic or latino ethnicity (15/22; 68.2%). Median weight was 38.5 kg. The median disease duration from the date of first diagnosis was 1.65 (range 0.1 – 11.8) years. A total of 17/19 patients (77.3%) reported previous non-biologic DMARD use (t_cm_SE_DMARD_CMP2), and 20/22 patients (90.9%) had previous biologic DMARD use (including previous use of TCZ). Although

all patients entering Part 2 of the study had received TCZ previously (either during Part 1 or commercially), the proportion of patients with previous biologic DMARD use at baseline was <100 % because 'previous use' refers to the period prior to Part 1 for those Part 2 patients who had previously participated in Part 1.

As it was a pre-requisite for study entry, all patients were in clinical remission of sJIA at baseline. The median JADAS-71 score at Part 2 baseline was 0.05 (mean 0.34), with a median of 0 (mean 0) active joints. Mean CRP and ESR values were 3.1 mg/L and 3.1mm/hr, respectively.

- **Numbers analysed**

Analysis Populations were defined as follows:

- All TCZ Population (Part 1) consists of all patients who received at least one dose of TCZ during Part 1
- All TCZ Population (Part 2) consists of all patients who received at least one dose of TCZ during Part 2
- Safety Population (Part 1) is a subset of the All TCZ population who received at least one dose of TCZ and had one safety assessment during Part 1
- Safety Population (Part 2) is a subset of the All TCZ population who received at least one dose of TCZ and had one safety assessment during Part 2
- PK population is a subset of the All TCZ population who received at least one dose of TCZ and had at least one valid PK result
- PD population is a subset of the All TCZ population who received at least one dose of TCZ and had at least one valid PD result

Table 3: Analysis Populations, Part 2 (All TCZ Population)

	TCZ IV 12 mg/kg Q3W or Q4W (N=7)	TCZ IV 8 mg/kg Q3W or Q4W (N=15)	All TCZ (N=22)
All TCZ Population	7	15	22
Safety Population	7	15	22
Total Exclusions	0	0	0
PK Population	7	15	22
Total Exclusions	0	0	0
PD Population	7	15	22
Total Exclusions	0	0	0

Q3W or Q4W indicates that where patients transition to Q4 dosing the data are summarised within one treatment group.

Program:
 root/clinical_studies/RO4877533/CDPT3363/WA28029/data_analysis/CSRFinal/prod/program/t_pop.sas
 Output: root/Clinical_studies/RO4877533/CDPT3363/WA28029/data_analysis/CSRFinal/prod/output/
 t_pop_ATC22_P2.out
 22JAN2020 11:55

Page 1 of 1

Source: CSR p 57

- **Outcomes and estimation**

Juvenile Arthritis Disease Activity Score (JADAS-71)

To enter Part 2 of the study, patients were required to have a JADAS-71 score of 3.8 or less at screening and baseline, and during the study at the time of switching from TCZ IV Q3W to TCZ IV Q4W.

JADAS-71 scores generally remained near the level of inactive disease (<1.0) for the majority of patients throughout the study during TCZ IV 8 mg/kg Q3W or Q4W dosing and TCZ IV 12 mg/kg Q3W or Q4W dosing. There were increases in the JADAS-71 scores at the time of sJIA flare as expected.

One patient had an increase in JADAS-71 at Week 33 which was not associated with an sJIA flare or fever due to sJIA. This increase in JADAS-71 was driven solely by the patient/parent's global assessment of overall wellbeing, and all other components of the composite score remained low at that visit.

JIA flare

Five of the 22 patients enrolled in Part 2 of the study experienced a flare, with one patient experiencing two flares (at consecutive study visits). Four patients experienced a flare while on TCZ IV Q3W dosing, and one of the seven patients who transitioned onto TCZ IV Q4W dosing flared at week 32 while on this treatment regimen.

During Part 2 TCZ IV Q3W dosing, there were 15 patients on 8 mg/kg TCZ and seven patients on 12 mg/kg TCZ. Three of the patients who flared during Q3W dosing were on 8 mg/kg TCZ, and one was on 12 mg/kg TCZ. The flares on Q3W dosing occurred at Week 9 (12 mg/kg), Week 12 (8 mg/kg), Week 15 (8 weeks after last dose of study drug; 8 mg/kg), and in one patient at Week 18 and 21 (8 mg/kg).

Two of these four patients who flared, withdrew from the study following the flare for lack of efficacy. One patient withdrew following the flare due to a concurrent SAE of hypertransaminasemia, and one patient was already in the process of withdrawing from the study for another reason at the time of the flare.

The patient who experienced two flares met the flare criteria at both Week 18 and 21 of the study; however the patient was assessed as flaring at Week 18.

Seven of the 22 patients in Part 2 of the study switched from TCZ IV Q3W to Q4W dosing, and one patient flared during Q4W dosing (8 mg/kg). This patient flared at Week 32 of Q4W dosing (Week 53 from Part 2 baseline), and withdrew from the study due to lack of efficacy following the flare.

Of the 17/22 patients who did not flare during TCZ IV Q3W or Q4W dosing, 13 completed Part 2 of the study. Two patients withdrew while in clinical remission of their sJIA, in order to give them a reduced TCZ dosing regimen outside of the study, and two patients withdrew for other reasons (protocol violation and needle phobia).

Fever due to sJIA

Based on the temperature measurement data collected during the study, there were no patients with fever due to sJIA during the study

One patient (8 mg/kg Q3W) was recorded as having a fever due to sJIA at Week 18 during an sJIA flare, (based on data collected by the external vendor)

JIA ACR Components Used in the Assessment of sJIA Flare

- **Physician Global Assessment Visual Analogue Scale**

Physician's global assessment of disease activity VAS was recorded on a scale of 0 - 100 mm, 0 mm for no arthritis symptoms and 100 mm for maximum arthritis symptoms.

The mean physician global assessment of disease activity score was <3 mm at Part 2 baseline and remained <5 mm throughout TCZ IV Q3W and TCZ IV Q4W dosing, apart from increases at specific time points driven by patients with sJIA flares.

- **Number of active joints**

Seventy-one joints were assessed for signs of active arthritis at each visit.

The mean number of joints with active arthritis (out of 71) was <0.1 at baseline of Part 2, and remained low throughout the study, during TCZ IV Q3W and Q4W dosing. There were increases in the number of joints with active arthritis at times of sJIA flare

Thirteen patients maintained zero joints with active arthritis throughout the entire Part 2 study period. The maximum number of active joints for a patient without flare was 5.

- **Number of joints with limitation of movement**

Sixty-seven joints were assessed for signs of limitation of movement during each visit.

The mean number of joints with limitation of movement (out of 67) was <0.3 at baseline of Part 2, and remained low throughout the study, during TCZ IV Q3W and Q4W dosing.

Limitation of movement in at least two joints, during a study visit for a patient contributed to the JIA flare calculation.

Systemic symptoms

- sJIA physical signs

The presence of specific physical examination findings that are associated with active sJIA (lymphadenopathy, rash (characteristic of patient's sJIA), pericardial rub, pleural rub, cushingoid appearance, hepatomegaly, and splenomegaly) were recorded at the time of physical examinations during the study.

Four patients had sJIA physical sign present at baseline.

Two patients developed a new sJIA physical sign during the study at the time of flare: One patient on Q3W dosing developed a rash (characteristic of patient's sJIA) at Week 21, and one patient on Q3W dosing developed lymphadenopathy at Week 15.

Three patients developed sJIA physical signs during the study, which were not associated with an sJIA flare. One patient on Q3W dosing developed cushingoid appearance, hepatomegaly, and splenomegaly at Week 9, one patient on Q3W dosing developed lymphadenopathy at Week 24, and one patient on Q3W dosing developed a rash (characteristic of patient's sJIA) at the Week 8 follow up visit. In all three patients, the sJIA signs were absent by the next study visit.

Patient reported outcomes

- **Childhood Health Assessment Health Questionnaire ne Disability Index (CHAQ-Di)**

The childhood health assessment questionnaire-disability index (CHAQ-DI) was recorded to evaluate functional ability as a scale of 0 (best) to 3 (worst).

The mean CHAQ Disability Index score was <0.05 (SD 0.09) at baseline of Part 2 of the study, and increased to a maximum of 0.34 (SD 0.97) at Week 21 during TCZ IV Q3W dosing then fell back down to <0.05 for the remainder of the study.

The mean CHAQ Disability Index score was zero throughout TCZ IV Q4W dosing.

There were increases in the CHAQ Disability Index score in 4 of the 6 flares which occurred during the study. In the other two flares, the CHAQ Disability Index score was zero at the time of flare.

- **Parents/patients global assessment of overall well-being**

Patient's (parent's/guardian's) overall assessment of their (child's) overall well-being was recorded on a 100 mm horizontal VAS scale, 0 for "very well" (symptom-free and no arthritis symptoms) and 100 for "very poor" (maximum arthritis disease activity).

The mean parent/patient global assessment of overall wellbeing score was <3 mm at baseline of Part 2 of the study, and remained <5 mm throughout TCZ IV Q3W dosing, apart from increases at specific time points which were driven by patients with sJIA flares.

One patient who had an increase in their parent/patient global assessment of overall wellbeing score which was not associated with a flare.

- **Pain VAS**

Pain VAS was assessed on a scale of 0 - 100 mm, 0 for no pain and 100 mm for very severe pain.

The mean patient pain index assessment VAS was <5 mm at baseline of Part 2 of the study and remained low throughout the study during TCZ IV Q3W and Q4W dosing.

Erythrocyte sedimentation rate

ESR values showed a high between and within patient variability over time, but all measured values remained below the ULN (15 mm/h) in both dosing groups and regardless to the dosing frequency.

In addition, there was no clear relationship between ESR levels and flare occurrence in the 12 mg/kg dosing group where only one patient flared. In the 8 mg/kg dosing group, flare occurred once just after an increase in ESR to 20 mm/hr in one patient on Q4W dosing and once just before an increase in ESR to 14 mm/hr in a patient on Q3W dosing. For one patient, both flares happened with normal ESR values comparable to baseline.

- **C-reactive protein**

Mean CRP levels at baseline for the Q3W dosing regimen were slightly higher in the 12 mg/kg group (4.8 mg/L) as compared with the 8 mg/kg group (2.3 mg/L), but not considering the median (0.2 mg/L in both dosing groups), including ranges which were quite similar. There was no clinically relevant increase in CRP levels over time when TCZ was administered Q3W.

One patient in the 12 mg/kg dosing group showed a transient increase at week 18 (up to 11 mg/L) without any flare, which returned to normal immediately thereafter. Overall, there were very limited changes in CRP levels measured over time.

Observations were quite similar following the Q4W dosing regimen. Mean CRP levels at baseline were slightly higher in the 8 mg/kg group (0.96 mg/L) as compared with the 12 mg/kg group (0.20 mg/L: note that only one patient switched from Q3W to Q4W in this dosing group). Nevertheless, median values were again similar across groups (0.2 mg/L), with one patient showing a value just above the ULN (4.75 mg/L). Only one patient presented with an increased value at Week 24 of the Q4W dosing period (up to 19.4 mg/L), which was back to normal immediately after, and which was followed by a flare. The mean value of 4 mg/L reported for that time point was mainly driven by this individual patient. Overall, CRP values barely fluctuated over time, remaining within a narrow range of values.

Interleukin-6

Overall, pre-dose IL-6 levels did not show significant fluctuation over time as compared to baseline values in patients dosed Q3W and Q4W, except in one patient in the 8 mg/kg Q3W dosing group who presented with a transient increase in IL-6 at Week 27.

Interleukin-6 Soluble Receptor

Mean serum sIL-6R levels over time did not show any significant nor sustained variation as compared to baseline values in both the Q3W and Q4W dosing regimen groups.

7.3. Discussion

TCZ treatment is associated with certain laboratory abnormalities, including thrombocytopenia, neutropenia, and liver enzyme abnormalities. Dose modification recommendations in sJIA are to stop TCZ dosing until the laboratory abnormality resolves. The purpose of this study was to investigate the use of less frequent dosing upon reinitiating treatment in patients who have achieved a high level of efficacy with TCZ but have experienced these laboratory abnormalities.

The study comprised a run-in phase (Part 1) and the main study (Part 2). Patients could enter Part 2 directly, or via Part 1. The objective of Part 1 was to increase enrolment into Part 2 by identifying patients with resolved laboratory abnormalities in Part 1 on the TCZ every two weeks (Q2W) regimen who would be eligible to participate in Part 2. Patients could also enter Part 2 directly, without having previously participated in Part 1.

In the run in evaluation period (Part 1) TCZ naive and non-naïve patients who met inclusion and no exclusion criteria with sJIA > 1 month were enrolled. Patients received TCZ according the approved posology i.e. TCZ IV dosed by body weight (12 mg/kg for patients <30kg; 8 mg/kg for patients ≥30 kg) Q2W up to 24 weeks or until they experienced a laboratory at which point they could be assessed for entry into Part 2.

In Part 2 of the study doses of 8 mg/kg for patients ≥30 kg and 12 mg/kg for patients <30 kg were used however as agreed with CHMP / EMA at Q3W or Q4W resp. in order to address the post approval measure (PAM) to investigate the dose reduction response to pre-defined laboratory abnormalities in sJIA patients. Thus patients were treated Q3W for up to 52 weeks, unless they experienced a pre-defined laboratory abnormality. Following the occurrence and resolution of a pre-defined laboratory abnormality, patients who had maintained adequate disease control, and had received a minimum of 5 consecutive Q3W infusions in Part 2 of the study, were moved to Q4W dosing of TCZ.

The design is acceptable.

Results

Nineteen 19 patients enrolled in Part 1, and finally 22 patients were enrolled into Part 2; 16 patients enrolled directly into Part 2, and an additional 6 patients entered via Part 1. Of these 22 patients, 7 patients completed the study under the in Part 2 of the study is rather small.

The key efficacy measures were Juvenile Arthritis Disease, Juvenile Idiopathic Arthritis (JIA) flare, and fever (attributable to sJIA).

JADAS-71 scores generally remained near the level of inactive disease (<1.0) for the majority of patients throughout the study during TCZ IV Q3W and TCZ IV Q4W dosing. There were increases in the JADAS-71 scores at the time of sJIA flare as expected.

Overall, sJIA continued to be well-controlled (no flare) in 17/22 patients (77%) during Part 2. Five patients (23%) experienced a flare during the study with one patient experiencing two flares (at consecutive study visits).

During TCZ IV Q3W dosing, three of the 15 patients on 8 mg/kg TCZ flared, and one of the seven patients on 12 mg/kg TCZ flared. The flares occurred at Week 9, Week 12, Week 15 (8 weeks after last dose of study drug), and in one patient at Week 18 and 21. One of the seven patients who transitioned to TCZ IV Q4W flared during Q4W dosing at Week 32 (week 53 from Part 2 baseline). The patient was receiving TCZ IV 8 mg/kg.

There were no patients who experienced fever due to sJIA during the study.

The mean values for each of the JADAS-71 components (physician global assessment VAS, patient/parent global assessment VAS, number of active joints, and ESR) were low at baseline and remained low throughout TCZ IV Q3W and Q4W dosing.

The mean CHAQ Disability Index score was <0.05 (SD 0.09) at the baseline of Part 2, increased to a maximum of 0.34 (SD 0.97) at Week 21 during TCZ IV Q3W dosing then fell back to <0.05 for the remainder of the study. The mean CHAQ Disability Index score was 0 throughout TCZ IV Q4W dosing.

The mean patient pain index assessment VAS was low at baseline and remained low throughout the study during TCZ IV Q3W and Q4W dosing. of inactive disease (<1.0) for the majority of patients throughout the study during TCZ IV Q3W and TCZ IV Q4W dosing. There were increases in the JADAS-71 scores at the time of sJIA flare as expected.

There were no clinically relevant increases changes in the pharmacodynamics parameters over time.

In conclusion, the data indicated that sJIA continued to be well-controlled during the reduced dosing frequency regimens of TCZ IV Q3W and Q4W. However it should be kept in mind that the data base is rather small, which precluded a robust conclusion.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

The Safety Population (Part 1) is a subset of the All TCZ population who received at least one dose of TCZ and had one safety assessment during Part 1.

The Safety Population (Part 2) is a subset of the All TCZ population who received at least one dose of TCZ and had one safety assessment during Part 2

Nineteen patients received TCZ IV Q2W in Part 1 of the study with a median duration of exposure of 25.9 weeks and a median of 13.0 doses. The dose intensity in Part 1 of the study ranged from 43% - 100% and the cumulative dose ranged from 930 mg - 5608 mg.

In Part 2 of the study, 22 patients received TCZ IV Q3W or Q4W with a median duration of exposure of 54.0 weeks and a median of 15.0 doses. The dose intensity ranged from 71% - 100% and the cumulative dose ranged from 923 mg - 10732 mg for the all TCZ population.

8.2. Results

Adverse event

In Part 1 of the study 16/19 patients (84.2%) experienced at least one AE, with a total of 70 AEs. The overall rate of AEs in Part 1 of the study was 653.6 events per 100 patient years (PY) (95% CI 509.5, 825.8).

The most common AEs in Part 1 of the study were in the Infections and Infestations System Organ Class (SOC) with 27 AEs in 10 patients. There were 8 AEs in Investigations; 5 AEs for Gastrointestinal Disorders; 4 AEs for Skin and Subcutaneous Tissue Disorders; 3 AEs for Eye Disorders; 6 AEs for Injury, Poisoning and Procedural Complications; 2 AEs for Blood and Lymphatic System Disorders; 2 AEs for ImmuneSystem Disorders; 4 AEs for Nervous System Disorders; 4 AEs for Respiratory, Thoracic and Mediastinal Disorders; 1 AE for Ear and Labyrinth Disorders, 1 AE for General Disorders and Administration Site Conditions; 1 AE for Hepatobiliary Disorders; and 2 AEs for Metabolism and Nutrition

Disorders. Upper Respiratory Tract Infection (4 cases) and Arthropod Bite (4 cases) were the most common AEs.

In Part 2 of the study 21/22 patients (95.5%) experienced at least one AE for a total of 113 AEs. The overall rate of AEs in Part 2 of the study was 551.0 events per 100 PY (95% CI 454.1, 662.4).

In the All TCZ group, there were 39 AEs for Infections and Infestations; 11 AEs for Injury, Poisoning, and Procedural Complications; 6 AEs for Musculoskeletal and Connective Tissue Disorders; 9 AEs for Skin and Subcutaneous Tissue Disorders; 14 AEs for Blood and Lymphatic System Disorders; 5 AEs for Gastrointestinal Disorders; 9 AEs in Investigations; 8 AEs in Respiratory, Thoracic, and Mediastinal Disorders; 2 AE for Ear and Labyrinth Disorders; 2 AEs for General Disorders and Administration Site Conditions; 1 AE for Hepatobiliary Disorders; 1 AE for Immune System Disorders; 1 AE for Metabolism and Nutrition Disorders; 1 AE for Neoplasms Benign, Malignant and Unspecified; 1 AE for Nervous System Disorders; 1 AE for Psychiatric Disorders; and 1 AE for Reproductive System and Breast Disorders.

The most common AEs were Nasopharyngitis (8 AEs); Leukopenia (7AEs); Upper Respiratory Tract Infection (5 AEs); Urinary Tract Infection (5 AEs); and Neutropenia (5 AEs).

Adverse events by intensity

In Part 1 of the study, 16/19 patients (84.2%) experienced an AE of which the maximum intensity was mild in 7 patients (36.8%), moderate in 6 patients (31.6%), and severe in 3 patients (15.8%). The severe AEs were hepatic enzyme increased (1 AE), neutropenia (1 AE), and haemophagocytic lymphohistiocytosis (1 AE).

In Part 2 of the study, 21/22 patients (95.5%) experienced an AE of which the maximum intensity was mild in 10 patients (45.5%), moderate in 10 patients (45.5%), and severe in 1 patient (4.5%). The severe AE was pneumonia in the TCZ IV 12 mg/kg Q3W treatment group.

Serious adverse events and deaths

In Part 1 of the study, one patient experienced one SAE of haemophagocytic lymphohistiocytosis (MAS) with a rate of 10.71 events per 100 PY (95% CI: 0.2, 52.0)

In Part 2 of the study, two patients experienced one SAE each. One patient was in the TCZ IV 8 mg/kg Q3W dosing group and experienced hypertransaminasaemia and the other patient was in the TCZ IV 12 mg/kg Q3W dosing group and experienced pneumonia. The overall rate of SAEs in Part 2 of the study was 9.8 events per 100 PY (95% CI 1.2, 35.2).

There were no deaths reported during Part 1 and Part 2 of the study.

Adverse events that led to withdrawal of study treatment

In Part 1 of the study two patients experienced AEs that led to withdrawal of study treatment. One patient experienced haemophagocytic lymphohistiocytosis which was determined to be not related to the study drug and received treatment. The second patient experienced increased hepatic enzymes which was determined to be related to the study drug. Both AEs were reported as recovered/resolved.

One patient experienced an AE that led to withdrawal of study treatment in Part 2 of the study. This patient experienced hypertransaminasaemia, which was determined to be unrelated to the study drug. At the time of withdrawal from the study, the SAE of hypertransaminasaemia had resolved.

Adverse events that led to dose modifications

Four patients in Part 1 of the study experienced 5 AEs that led to study drug interruption. The AEs leading to study drug interruption were infections (3 events in two patients) and elevated liver enzymes (2 events

in 2 patients). There were no events that led to the dose being reduced. None of the patients had the study drug withdrawn because of these events.

In Part 2 of the study, nine patients (40.9%) experienced 16 AEs which led to study drug interruption. The most common AEs leading to study drug interruption were infections (8 events in 4 patients), neutropenia (3 events in 3 patients) and leukopenia (2 events in 2 patients). Three patients had their dose of study drug reduced. None of the patients had the study drug withdrawn because of these events.

Adverse events of special interest / selected adverse events

- **Serious infections**

In Part 2 of the study, there was one SAE of pneumonia, giving an overall rate of 4.9 events per 100 PY (95% CI 0.1, 27.2). This SAE of pneumonia was assessed as severe in intensity, unrelated to the study drug and had an outcome of recovered/resolved.

Hepatic Events

There was one non-serious hepatic AE of hepatic steatosis in Part 1 of the study that was ongoing at the time of last contact with the patient. The study drug was not changed in response to this event, and the patient continued to move onto Part 2 of the study.

There were no hepatic AEs in Part 2 of the study.

Bleeding Events

There were no serious bleeding events in Part 1 or Part 2 of the study.

There was one moderate, non-serious bleeding AE of Contusion in Part 1 of this study which was recovered/resolved and did not require any change to the study drug.

In Part 2 of the study, there were three patients in the TCZ IV 8 mg/kg Q3W dosing group who experienced a bleeding event during the study. All three cases were non-serious, mild and resolved without change to study drug administration.

Other AESIs

There were no events reported for other AESIs in Part 1 or Part 2 of the study including malignancies, opportunistic infections, hypersensitivity reactions, anaphylactic reactions, gastrointestinal perforations, demyelinating disorders, myocardial infarction, and stroke. There were no Hy's Law or STIAMP cases.

Selected events

Infection

Ten patients (52.6%) experienced twenty-seven infection AEs in Part 1 of the study, giving a rate of 252.1 events per 100 PY. The most common infections in Part 1 of the study were upper respiratory tract infection (4 events), cystitis (3 events), and pneumonia (3 events).

In Part 2 of the study, there were 17 patients (77.3%) with 39 infections in the all TCZ group, giving a rate of 190.2 events per 100 PY (95% CI 135.2, 259.9). The most common infection AEs were nasopharyngitis (8 events), upper respiratory tract infection (5 events) and urinary tract infection (5 events). In Part 2 of the study, there was one serious infection of pneumonia.

Neutropenia

There was one neutropenia AE reported in Part 1 of the study. The AE was severe in intensity, resolved and the patient continued into Part 2 of the study.

There were five AEs of neutropenia in four patients reported in Part 2 of the study, one in the TCZ IV 12 mg/kg Q3W dosing group and four in the TCZ IV 8 mg/kg Q3W dosing group. They were all mild to moderate in intensity and resolved. In two of the patients the TCZ dose was reduced, in one patient TCZ was interrupted and in one patient the dose was not changed. The patient with a neutropenia AE reported in Part 1 of the study did not have an AE of neutropenia in Part 2 of the study.

Thrombocytopenia

There were no thrombocytopenia events in Part 1 of the study.

There was one thrombocytopenia AE in Part 2 of the study in the TCZ IV 8 mg/kg Q3W dosing group. This AE was mild in intensity and resolved.

Macrophage activation Syndrome

In Part 1 of the study, one patient experienced a serious and severe event of haemophagocytic lymphohistiocytosis (MAS) and withdrew from the study due to this event. The event was assessed as unrelated to the study drug and the event resolved following treatment.

No events of MAS occurred in Part 2 of the study.

Laboratory findings

Haematology

- **Lymphocytes**

In Part 1 of the study, 18 patients (94.7%) had a normal lymphocyte count at baseline, and one patient (5.3%) had a Grade 1 low lymphocyte count. During Part 1, most patients (89.5%) had a post-baseline value of Grade 0, one patient had a lymphocyte (low) value of Grade 1, and one patient had a value of Grade 4.

In Part 2 of the study, 21 patients (95.5%) had a normal lymphocyte count at baseline, and one patient (4.5%) had a missing baseline value. During Part 2 of the study, 16 patients (72.7%) had a post-baseline value of Grade 0, three patients (13.6%) had values of Grade 1, one patient (4.5%) had a value of Grade 2, and two patients (9.1%) had values of Grade 4

- **Neutrophil counts**

All patients had a normal neutrophil count at baseline in Part 1 of the study. Post-baseline, 14 patients (73.7%) maintained a neutrophil count within the normal range, while a worst value of Grade 1, 2, or 3 neutropenia was reported in 1 (5.3%), 2 (10.5%) and 2 patients (10.5%), respectively. Both patients who had Grade 3 neutropenia during Part 1 had Grade 3 neutropenia at a single time point. There were no patients with Grade 4 low neutrophil counts during Part 1

At baseline in Part 2 of the study, 17 patients (77.3%) had a normal neutrophil count whereas 2 patients (9.1%) had Grade 1, 2 patients (9.1%) had Grade 2, and in one patient (4.5%) the baseline neutrophil count was missing. Post-baseline, 10 patients (45.5%) had a normal neutrophil count, while a worst value of Grade 1, Grade 2, or Grade 3 neutropenia was reported in 4 (18.2%), 4 (18.2%), and 3 patients (13.6%), respectively. Of the three patients who had Grade 3 neutropenia during Part 2 of the study, two had Grade 3 neutropenia at a single time point, while one patient had non-consecutive Grade 3 neutropenia. There were no patients with Grade 4 low neutrophil counts during Part 2 of the study.

During Part 2 of the study, there was one serious infection (pneumonia). This SAE did not occur within 15 days of a low neutrophil count. There were no serious infections during Part 1 of the study.

- **Platelet Counts**

In Part 1 of the study, all 19 patients had a normal platelet count at baseline. During Part 1, a worst value of Grade 1 was reported in two patients (10.5%) and Grade 2 in one patient (5.2%). The patient with Grade 2 thrombocytopenia experienced a Grade 1 low platelet count at Week 8 and on Weeks 20 and 22 had a Grade 2 low platelet count. The lowest value was $57 \times 10^9/L$. After this event, the values fluctuated between Grades 0 and 1. The final value was Grade 1. This patient did not have any bleeding AEs during the study.

At baseline of Part 2 of the study, 20 patients (90.9%) had a normal platelet count, with 1 patient (4.5%) having a Grade 1 low platelet count, and one patient (4.5%) having a missing baseline platelet count. Post baseline during Part 2 of the study, 18 patients (81.8%) retained a normal platelet count, and four patients (18.2%) had a Grade 1 low platelet count.

There were no Grade 3 or 4 low platelets counts reported during Part 1 or Part 2 of the study of the study. There were also no serious bleeding events in Part 1 or Part 2 of the study.

Chemistry

Liver Enzymes

Changes from baseline in liver enzyme values of Grade 2 and higher were uncommon.

In both Part 1 and Part 2 of the study there were no patients who had simultaneous elevations $\geq 3 \times$ ULN in ALT or AST and $\geq 2 \times$ ULN in total bilirubin (laboratory criteria for Hy's Law). There were no serious hepatic AEs in Part 1 or Part 2 of the study.

- **ALT**

At baseline in Part 1 of the study, 18 patients (94.7%) had ALT values within the normal range, and one patient (5.3%) had a Grade 1 elevation. Post baseline in Part 1 of the study, most patients (16/19: 84.2%) had ALT values of \leq Grade 1; one patient (5.3%) had a Grade 2 ALT elevation and two patients (10.5%) had a Grade 3 ALT elevation. One of the Grade 3 elevations occurred at a single time point and was reported as a non-serious severe AE (hepatic enzyme increased) which led to the patient withdrawing from the study. The other Grade 3 elevation occurred in a patient during an SAE of MAS.

At baseline in Part 2 of the study, 21 patients (95.5%) had an ALT within the normal range, and one patient (4.5%) had a Grade 1 elevation. Post baseline in Part 2 of the study, 20 patients (90.9%) had ALT concentrations of \leq Grade 1. One patient (4.5%) had a Grade 2 elevation and one patient (4.5%) had a Grade 4 elevation. The patient with a Grade 4 elevation had an SAE of hypertransaminasemia and withdrew from the study due to this event.

- **AST**

All 19 patients had a normal AST level at baseline in Part 1 of the study. Post baseline during Part 1, 11 patients (57.9%) had their AST remain within the normal range, Six patients (31.6%) had a Grade 1 elevation, one patient (5.3%) had a Grade 2 elevation and one patient (5.3%) had a Grade 3 elevation (Table 23). The Grade 3 elevation occurred in the patient who had an SAE of MAS.

All 22 patients had a normal AST level at baseline in Part 2 of the study. Post baseline during Part 2 of the study, 16 patients (72.7%) had AST remain within the normal range, five patients (22.7%) had a Grade 1 elevation and one patient (4,5%) had a Grade 2 elevation.

- **Bilirubin**

At baseline of Part 1, 14 patients (73.7%) had normal bilirubin levels, two patients (10.5%) had a Grade 1 elevation and three patients (15.8%) had a missing value. Post baseline during Part 1, 16 patients

(52.6%) total had a bilirubin level within the normal range, one patient (5.3%) had a Grade 1 elevation and two patients (10.5%) had a Grade 2 elevation. Of the three patients (15.8%) who had missing bilirubin values at baseline, all had post-baseline values of Grade 0.

At baseline of Part 2 of the study, 18 patients (81.8%) had normal bilirubin levels, one patient (4.5%) had a Grade 1 elevation, one patient (4.5%) had a Grade 2 elevation, and two patients (9.1%) had missing values. Post baseline during Part 2 of the study, 17 patients (77.3%) in total had their bilirubin remain within the normal range, two patients (9.1%) had a Grade 1 elevation and three patients (13.6%) had a Grade 2 elevation. Of the two patients (9.1%) (1 in each body weight group) who had missing bilirubin values at baseline, both of these patients had Grade 0 values post-baseline.

There were no Grade 3 or 4 elevations in bilirubin during Part 1 or Part 2 of the study.

- **Lipid Parameters**

No patients experienced either an elevated total cholesterol (> 200 mg/dL) or an elevated LDL (\geq 130 mg/dL) in Part 1 or Part 2 of the study.

Vital Signs

The majority of the patients (14/19: 73.7%) in Part 1 of the study did not experience abnormally high systolic or diastolic blood pressure (BP) and none of the patients had low systolic or diastolic blood pressure. Most of the patients (17/19: 89.5%) did not experience abnormally high or low heart rates. For 10/19 patients (52.6%), their weight did not increase >10% and for most of the patients (18/19: 94.7%) their weight did not decrease >10% in Part 1 of the study. Body temperature did not increase to over 38°C for any of the patients in Part 1 of the study.

In Part 2 of the study, most of the patients did not experience an increase or decrease in systolic or diastolic BP. None of the patients experienced an abnormally high heart rate and only one patient (4.5%) experienced low heart rate in the TCZ IV 8 mg/kg dosing group. Most of patients (21/22: 95.5%) in Part 2 of the study did not experience a decrease of >10% in their weight during the study, however, 13/22 patients (59.1%) experienced an increase of >10% in their body weight. No abnormal temperature increases above 38°C were reported for any of the patients.

Chest X-rays and Purified Protein Derivative Tests

There were no abnormal chest X-rays during Part 1 or Part 2 of the study.

In Part 1 of the study, one patient (5.2%) had a positive PPD skin test during screening on Day -14. There were no abnormal positive PPD skin tests during screening in Part 2 of the study.

Immunogenicity

In Part 2 of the study, no patient presented with positive titres of anti-TCZ antibodies.

Only one patient in Part 1 of the study showed positive titres at baseline, which were negative at Week 8; this patient was receiving TCZ prior to entering Part 1. Hence, there were no ADAs observed during this study.

Part 2:

Table 4: Overview of key safety and efficacy data by individual patients

Patient No.	Participation in Part 1	No. of Q3W doses received	No. of Q4W doses received	Disposition in Part 2	Reason for Discontinuation	Efficacy: sJIA Flare	SAEs (Part 2 only)	Laboratory Abnormalities		
								Criteria for study entry ¹	During TCZ Q3W ²	During TCZ Q4W ²
████	No	3	-	Discontinued	LOE	Flare: Wk 9 Q3W	-	Neutropenia	ALT/AST increased	Not applicable
████	Yes	7	8	Discontinued	LOE	Flare: Wk 32 Q4W	-	ALT/AST increased	Thrombocytopenia, AST increased	AST increased
████	Yes	12	4	Completed	-	-	-	ALT/AST increased	ALT/AST increased	ALT/AST increased
████	Yes	18	-	Completed	-	-	-	Neutropenia	-	Not applicable
████	No	18	-	Completed	-	-	-	ALT/AST increased	-	Not applicable
████	No	7	10	Completed	-	-	-	Neutropenia	Neutropenia	ALT/AST increased, Neutropenia
████	No	5	-	Discontinued	AE (Hypertransaminasemia)	Flare: Wk 12 Q3W	Hypertransaminasemia (onset SD 106 during TCZ Q3W; resolved; study drug withdrawn)	Neutropenia	Neutropenia, ALT/AST increased	Not applicable
████	No	7	-	Discontinued	Other (sJIA flare)	Flare: Wk 18+21 Q3W	-	Neutropenia	ALT increased	Not applicable
████	No	18	-	Completed	-	-	-	ALT increased	-	Not applicable
Patient No.	Participation in Part 1	No. of Q3W doses received	No. of Q4W doses received	Disposition in Part 2	Reason for Discontinuation	Efficacy: sJIA Flare	SAEs (Part 2 only)	Laboratory Abnormalities		
								Criteria for study entry ¹	During TCZ Q3W ²	During TCZ Q4W ²
████	No	3	-	Discontinued	WD by Patient	Flare: Wk 15 Q3W (8 wks after last study drug dose)	-	Thrombocytopenia	-	Not applicable
████	Yes	5	10	Completed	-	-	-	ALT/AST increased	AST increased	-
████	No	5	10	Completed	-	-	-	ALT increased	Neutropenia ³ Thrombocytopenia ³	-
████	No	17	-	Completed	-	-	-	ALT increased	ALT increased	Not applicable
████	No	4	11	Completed	-	-	-	Neutropenia	Neutropenia	Neutropenia
████	No	7	10	Completed	-	-	-	ALT/AST increased	Neutropenia	Neutropenia
████	Yes	12	-	Completed	-	-	-	ALT/AST increased, Neutropenia	-	Not applicable
████	No	17	-	Completed	-	-	-	ALT/AST increased	--	Not applicable
████	No	8	-	Discontinued	Physician Decision (Q4W dosing outside of protocol)	-	-	ALT increased	-	Not applicable

Patient No.	Participation in Part 1	No. of Q3W doses received	No. of Q4W doses received	Disposition in Part 2	Reason for Discontinuation	Efficacy: sJIA Flare	SAEs (Part 2 only)	Laboratory Abnormalities		
								Criteria for study entry ¹	During TCZ Q3W ²	During TCZ Q4W ²
████	No	7	-	Discontinued	Physician Decision (Q4W dosing outside of protocol)	-	-	ALT/AST increased	-	Not applicable
████	No	7	-	Discontinued	Protocol Deviation (medical history)	-	-	ALT/AST increased	ALT increased	Not applicable
████	No	9	-	Discontinued	Physician Decision (needle phobia)	-	-	Neutropenia	-	Not applicable
████	Yes	18	-	Completed	-	-	Pneumonia (onset SD 289 during TCZ Q3W; resolved)	ALT increased	-	Not applicable

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LOE = lack of efficacy; Q3W = every three weeks, Q4W = every four weeks; SAE = serious adverse event; SD = study day; sJIA = systemic juvenile idiopathic osteoarthritis; TCZ= tocilizumab; WD = withdrawal; Wk = week

Outputs: L_ex_SE_P2, L_ds_disc_ATCZ2_P2, L_ef_core_ATCZ2_P2, L_ae_SE_P2, L_mh_SE_MHP2, L_lb_neutr_SE_P1, L_lb_elev_SE_P1, L_lb_plt_SE_P1, L_lb_neutr_SE_P2, L_lb_elev_SE_P2, L_lb_plt_SE_P

¹To enter Part 2 of the study, patients had to meet the laboratory abnormality inclusion criteria as specified in protocol Table 5: neutropenia (ANC 0.5 to 1.0 × 10⁹/L), thrombocytopenia (Platelets 50 to 100 × 10⁹/L), or elevated liver enzymes (ALT/AST > 1 to 3 × ULN). For patients enrolled directly into Part 2, laboratory abnormality inclusion criteria were recorded on the medical history eCRF page; for patients enrolled from Part 1 into Part 2 of the study, the lab abnormality was recorded in the Part 1 laboratory data.

8.3. Discussion

There were no new or unexpected safety events observed during this study. The types of adverse event observed in this study during Part 1 (TCZ Q2W) and Part 2 (TCZ Q3W or Q4W) were consistent with AEs observed in other TCZ sJIA studies. Most patients in the study had at least one AE over the course of the entire study (84.2% of patients in Part 1 over a median 0.7 years of treatment exposure, and 95.5% of patients in Part 2 over a median of 1.1 years treatment exposure). The majority of these AEs were mild or moderate in intensity. AEs in the Infection and Infestation SOC were the most frequent AEs reported in the study (52.6% of patients in Part 1 of the study; 77.3% of patients in Part 2 of the study).

There were no deaths during this study. There were 3 serious adverse events (SAEs) during the course of the study (1 event of haemophagocytic lymphohistiocytosis in Part 1 of the study, and 1 event each of hypertransaminaemia and pneumonia in Part 2 of the study). Two of these SAEs resulted in discontinuation of study drug, and all 3 SAEs were later reported recovered/resolved. T

here were 3 AEs in 3 patients leading to withdrawal from study treatment; 2 (10.5%) occurred in Part 1 (one was the SAE of haemophagocytic lymphohistiocytosis, and the other was increased hepatic enzymes) and 1 (4.5%) occurred in Part 2 (SAE of hypertransaminaemia).

There were no cases of anaphylaxis based on the criteria of either Anaphylactic Reactions (SMQ Narrow) or Anaphylactic Reactions (Sampson's Criteria).

There were no cases that met the predefined AESI definition for demyelinating disorders, gastrointestinal perforations, hypersensitivity reactions, malignancies, myocardial infarctions, opportunistic infections, or stroke.

There was one event of MAS (haemophagocytic lymphohistiocytosis) in Part 1 of the study.

There were neither cases of STIAMP nor cases that met Hy's Law criteria reported in either Part 1 and 2.

Grade 2 and higher changes in laboratory test values from baseline were uncommon. There was no association between Grade 3 low neutrophil counts and serious infections, and no association between elevations in ALT or AST and serious hepatic injury events.

All patients entering Part 2 had previous laboratory abnormalities (neutropenia, thrombocytopenia, or elevated liver enzymes) as required per the protocol. Of the 22 patients in Part 2, 12 (54.5%) experienced a protocol defined laboratory abnormality during Q3W or Q4W dosing, and 10 (45.5%) patients did not.

There were no new safety concerns observed.

Conclusion

The safety outcomes from this study were similar to those achieved in other studies with TCZ IV Q2W and were consistent with the known safety profile of TCZ IV in sJIA. No new or unexpected safety concerns were observed.

A pre-requisite entering Part were previous laboratory abnormalities (neutropenia, thrombocytopenia, or elevated liver enzymes) as required per the protocol. sJIA continued to be well-controlled (no flare) during TCZ Q3W and Q4W dosing in 17 / 22 patients, 5 % patients (23%) patients did experience a flare during Part 2 of the study. Of note, after experiencing a protocol-defined laboratory abnormality to qualify for study entry, about half of the patients did not experience any further such abnormalities.

The study showed that sJIA patients who had experienced a laboratory abnormality (low neutrophils, low platelets, or increased ALT or AST) during IV TCZ Q2W treatment could maintain efficacy during an increased dosing interval of TCZ IV Q3W or Q4W, however, the MAA concluded that the data are not sufficient to introduce an SPC amendment on advice on dose adjustment in sJIA patients who experience laboratory abnormalities. Instead the MAH propose an administrative amendment:

Original Text:

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

Proposed Revision:

There are insufficient clinical data to assess the impact of a tocilizumab dose reduction in sJIA patients who have experienced laboratory abnormalities.

This approach is accepted.

8.4. Direct Healthcare Professional Communication

N/A

9. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

The submission included a revised EU-RMP (version 26). Rationale for submitting an updated RMP: This RMP version 26.0 reflects updates to study status for studies WA28029 (ARTHUR) and WA22480 (ARTIS) (both PASS Category 3 studies).

Summary of significant changes in this RMP:

- Updated study status from 'Ongoing' to 'Completed' for PASS Category 3 studies WA28029 (ARTHUR) and WA22480 (ARTIS) in the following Sections:
 - Section III.2 – Additional PV activities;
 - Section III.3 – Summary Table of Additional Pharmacovigilance Activities;
 - Section V.3 – Summary of Risk Minimization Measures;
 - Annex 2 – Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme.
- Inclusion of key results from studies WA28029 (ARTHUR) and WA22480 (ARTIS) in Section III.2 – Additional PV activities.
- Post-marketing exposure in the RMP was updated to align with information presented in the 2019 RoActemra PSUR/PBRER (Report No. 1093173; reporting interval 11 April 2018 to 10 April 2019).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The following changes to the RMP are recommended (new text **underlined and in bold**, deleted text is crossed out "~~deleted text~~"):

~~Studies ARTIS (WA22480) and RABBIT (ML28664, formerly tracked as GA28719) are investigating~~ **The** safety concerns of serious infections, complications of diverticulitis (including GI perforation), serious hypersensitivity reactions, neutropenia, thrombocytopenia and the potential risk of bleeding, hepatotoxicity, elevated lipid levels and potential risk of cardiovascular/cerebrovascular events, malignancies and demyelinating disorders in RA patients **are being investigated in ongoing Study RABBIT (ML28664, formerly tracked as GA28719). These safety concerns were also investigated in the completed Study WA22480 (ARTIS).** Both are EU registries for epidemiological data (Table 22 and Table 23).

Study WA28029 **investigates** (ARTHUR) **investigated** the possibility of dose reduction for laboratory abnormalities (low platelets, low neutrophil, and elevated liver transaminase levels), in sJIA patients (Table 24). The **ongoing** pediatric registry (WA29358) investigates long-term safety and efficacy data in pJIA patients.

RMP-Table 22 WA22480- (ARTIS) registry study

Study/activity short name and title: WA22480- (ARTIS) registry study: a nationwide safety monitoring of tocilizumab (Actemra®) treatment in patients with rheumatic diseases in Sweden.
Rationale and Study Objectives: To provide long term safety data from the use of TCZ in Sweden for RA patients
Study design: Phase IV, prospective observational cohort study
Study populations: Every person treated with TCZ with RA or any other rheumatic disease, in Sweden.
Milestones: First Patient First Visit: 1999 Annual updates will be provided in the PSUR Last Patient Last Visit: Completed Final CSR Report : Q4 2019 (Study completed) Key Results: <u>The final report for this study described the relative occurrence of a series of pre-defined safety outcomes in 2068 Swedish patients with RA treated with tocilizumab, or with other anti-rheumatic treatments, compared to the general Swedish population.</u> <u>The results illustrate risks associated with the treated disease or treatment context rather than with specific treatments, and also the marked potential for, and effects of, channeling to or away from different treatments. Whilst accommodating known or measurable confounding/selection factors, these results are thus liable to residual or unmeasured confounding or selection.</u> <u>With respect to tocilizumab, the overall pattern of risks and relative risks that emerges from these analyses is that of no new safety signals, and of risks that vary across treatment contexts and that seem to be more dependent on the treatment context in which tocilizumab was used/not used than on the individual biologic that was chosen.</u>
RA=Rheumatoid Arthritis; TCZ=Tocilizumab

RMP Table 24 WA28029 (ARTHUR)

Study/activity short name and title: A phase IV study to evaluate decreased dose frequency in patients with active systemic juvenile arthritis (sJIA) who experience laboratory abnormalities during treatment with tocilizumab
Rationale and study objectives: To investigate the use of less frequent dosing upon reinitiating treatment in patients who have achieved a high level of efficacy with TCZ but have experienced laboratory abnormalities (including thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients.
Study design: A 96-week, two-part, phase IV study to explore the efficacy, safety, pharmacokinetics, pharmacodynamics and immunogenicity of reduced dosing frequency of TCZ in patients with adequately controlled sJIA who have experienced a laboratory abnormality which has resolved..
Study populations: Children aged 2 years up to and including aged 17 years with sJIA \geq 1 month and currently receiving TCZ who have experienced a predefined, resolved laboratory abnormality.
Milestones: First Patient First Visit: June 2013 Last Patient Last Visit: Q4 2019 Final CSR: May April 2020 (Study completed) Key Results: <u>Study WA28029 (ARTHUR) was a 52-week study (Part 2), preceded by a run-in phase (Part 1) of 24 weeks. During the run-in phase (Part 1) patients received TCZ IV Q2W (8 mg/kg or 12 mg/kg depending on body weight), and in the main study (Part 2) patients received TCZ IV Q3W or Q4W dosing (8 mg/kg or 12 mg/kg depending on body weight). Patients could enroll in the run-in period or directly in the main study. Patient exposure included all patients enrolled in the run-in period or the main study. This included 19 patients enrolled in the run-in period and 22 patients enrolled in the main study. This study showed that sJIA patients who had experienced a laboratory abnormality (low neutrophils, low platelets, or increased ALT or AST) during IV TCZ Q2W treatment could maintain efficacy during an increased dosing interval of TCZ IV Q3W or Q4W. In addition, after experiencing a protocol-defined laboratory abnormality to qualify for study entry, approximately half of the patients did not experience any further such abnormalities. However, some patients did flare, and some did experience laboratory abnormalities on the Q3W or Q4W regimens, so no clear conclusions can be made.</u>
AE=adverse event; CSR=clinical study report; JADAS= juvenile arthritis disease activity score; PD= pharmacodynamics; sJIA=systemic juvenile idiopathic arthritis; Q2W= once every two weeks; Q3W=once every three weeks; Q4W= once every four weeks; RA=rheumatoid arthritis; TCZ = tocilizumab

9.1. Overall conclusion on the RMP

The changes to the RMP are acceptable.

10. Changes to the Product Information

In summary, it can be said that the study ultimately only led to formal changes of the EU-RMP (see above) and the SmPC of RoActemra (tocilizumab).

The Package Leaflet (PL) needs no update.

As a result of this variation, section 4.2 of the SmPC are being updated. The following changes to the SmPC are proposed and recommended (new text **underlined and in bold**, deleted text is crossed out "~~deleted text~~");

Section 4.2 Posology and method of administration (*abbreviated*)

Special populations (Paediatric patients/sJIA Patients)

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients (*-Liver enzyme abnormalities; -Low absolute neutrophil count (ANC); -Low platelet count*).

~~Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in sJIA patients.~~ **There are insufficient clinical data to assess the impact of a tocilizumab dose reduction in sJIA patients who have experienced laboratory abnormalities.**

11. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 23 July 2020