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SCIENCE MEDICINES HEALTH

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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

RoActemra

tocilizumab

Procedure no: EMEA/H/C/000955/P46/062

Note

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



Table of contents

1. Introduction	3
2. Scientific discussion	3
2.1. Information on the development program.....	3
2.2. Information on the pharmaceutical formulation used in the study.....	3
2.3. Clinical aspects	3
2.3.1. Introduction	3
2.3.2. Clinical Pharmacology	3
2.3.3. Clinical study	10
Description	10
Methods	10
Results.....	13
2.3.4. Discussion on clinical aspects	33
3. CHMP overall conclusion and recommendation.....	33
Fulfilled:	34

1. Introduction

On 01.07.2022, the MAH submitted a completed paediatric study RoActemra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study "Long-Term Extension Study to Evaluate the Safety and Efficacy of Subcutaneous Tocilizumab in Patients With Polyarticular-Course and Systemic Juvenile Idiopathic Arthritis, WA29231 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

N/A

CHMP comment

The formulation used in the study is authorised in the study population.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study WA29231 "Long-Term Extension Study to Evaluate the Safety and Efficacy of Subcutaneous Tocilizumab in Patients With Polyarticular-Course and Systemic Juvenile Idiopathic Arthritis"

At the time of the approval of final CSR, the bioanalytical reports were not yet available and could not be appended. An Addendum was provided including the final bioanalytical reports for PK/PD human serum samples and ADA in human serum samples. The final study results included exploratory PK and PD analyses to assess longterm effects.

2.3.2. Clinical Pharmacology

Bioanalytics

(Bioanalytical Report: 1116209 - Addendum)

Pharmakokinetics

The PK analysis was performed using a database of 763 PK samples collected in a total of 82 patients (44 pJIA patients and 38 sJIA patients).

pJIA

A graphical comparison of the distribution of trough concentrations before (Study WA28117) and during LTE Study WA29231 was performed by dosing regimen and overall showed a similar spread of concentrations within each dosing group and when comparing both dosing regimens. In WA29231, the

observed mean trough concentration-time profiles of TCZ in pJIA patients administered with Q2W or Q3W SC TCZ 162 mg were constant and in the same range over time, with no significant difference considering variability.

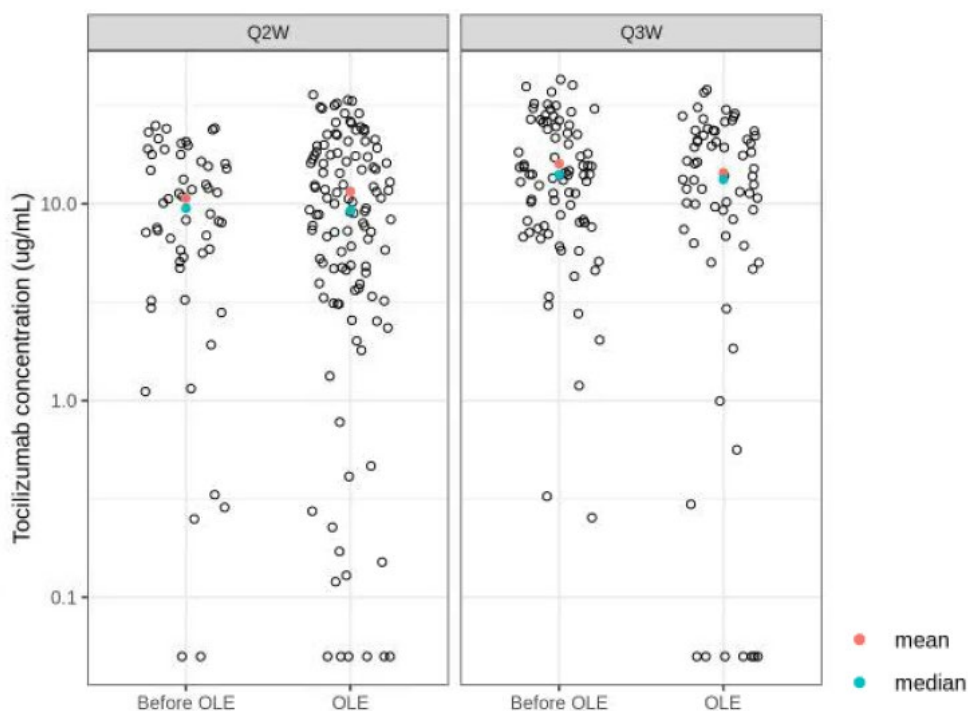


Figure 1 Distribution of Trough in pJIA Patients in Study WA28117 (before OLE) and WA29231 (OLE) (Semi-Log), PK Population

The observed median (range) trough concentration in Study WA29231 was 9.235 (0.050-35.80) ng/mL in the Q2W dosing regimen, as compared to 9.495 (0.050-25.00) ng/mL considering the last 3 samples at trough reported in WA28117. For Q3W dosing, the observed median (range) trough concentration in Study WA29231 was 13.30 (0.050- 38.00) ng/mL, as compared to 14.05 (0.254-42.8) ng/mL in WA28117.

The observed mean trough concentration-time profiles of TCZ in pJIA patients administered with Q2W or Q3W SC TCZ 162 mg were constant and in the same range over time, with no significant difference considering variability. The mean concentrations in the Q3W dosing group were lowest at Week 144; however, these results are based on data from a small number of patients (n = 4) with values in the lower end of the concentration spread and therefore, are considered inconclusive.

Mean concentrations were higher in the Q3W than in the Q2W dosing group at most time points, which is similar to what was observed in WA28117 and could be explained by the higher exposure observed in lower body weight patients administered with flat doses of SC TCZ related to the body weight effect on TCZ PK.

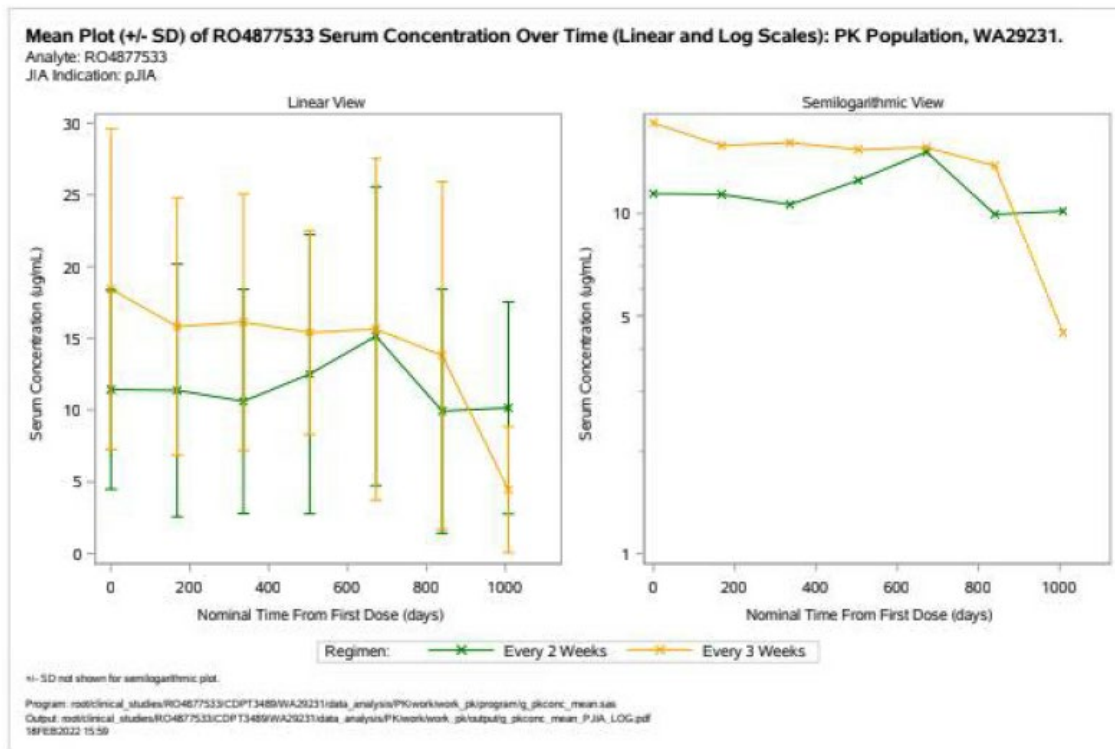


Figure 2 Mean TCZ Serum Concentrations vs Time in pJIA Patients in Study WA29231 (Linear and Log)

sJIA

The graphical comparison of the distribution of trough concentrations before (Study WA28118) and during LTE Study WA29231 showed overall a similar spread of concentrations within each dosing group and when comparing QW, Q10D and Q2W dosing regimen. In WA29231, the observed mean trough concentration-time profiles of TCZ in sJIA patients administered with QW, Q10D or Q2W SC TCZ 162 mg were steady and in the same range over time, with no significant difference in variability.

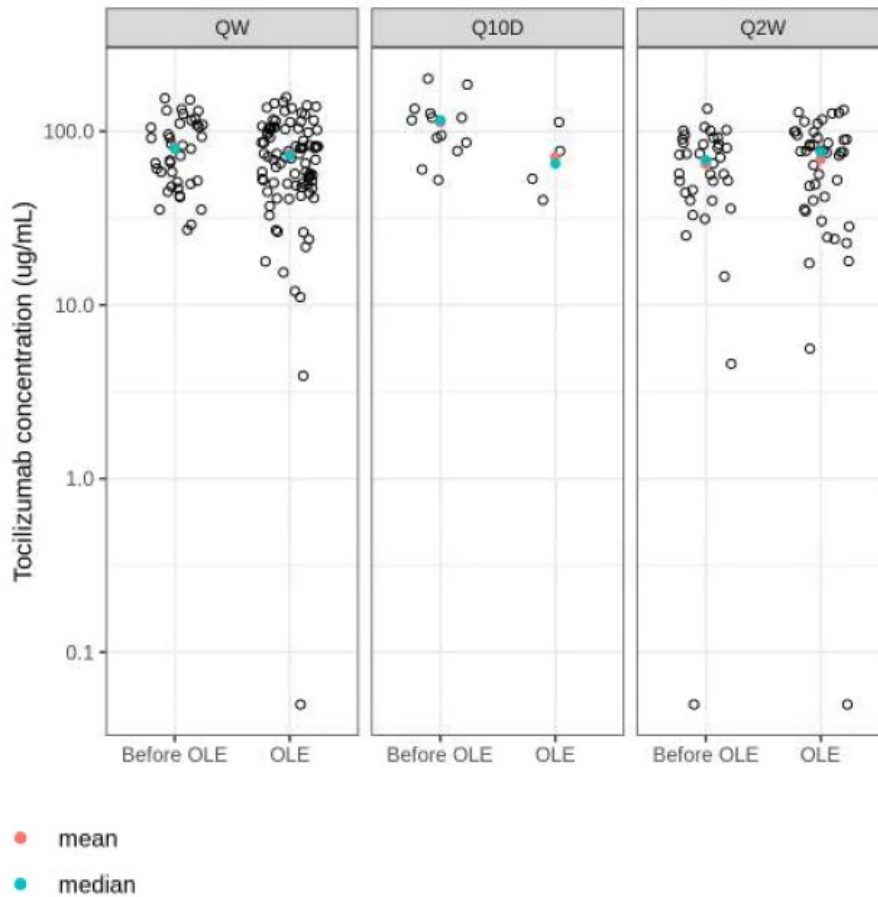


Figure 3 Distribution of Ctrough in sJIA patients in Study WA28118 (before OLE) and WA29231 (OLE) (Semi-Log)

The observed median (range) trough concentration in Study WA29231 was 72.90 (0.050-157.0) ng/mL in the QW dosing regimen, as compared to 79.50 (27.10-155) ng/mL considering the last 3 samples at trough reported in WA28118. For Q10D dosing, the observed median (range) trough concentration in Study WA29231 was 65.20 (40.20-113) ng/mL, as compared to 116 (52.50-201) ng/mL in WA28118. For Q2W dosing, the observed median (range) trough concentration in Study WA29231 was 75.80 (0.050-133) ng/mL, as compared to 68.05 (0.050-135) ng/mL in WA28118.

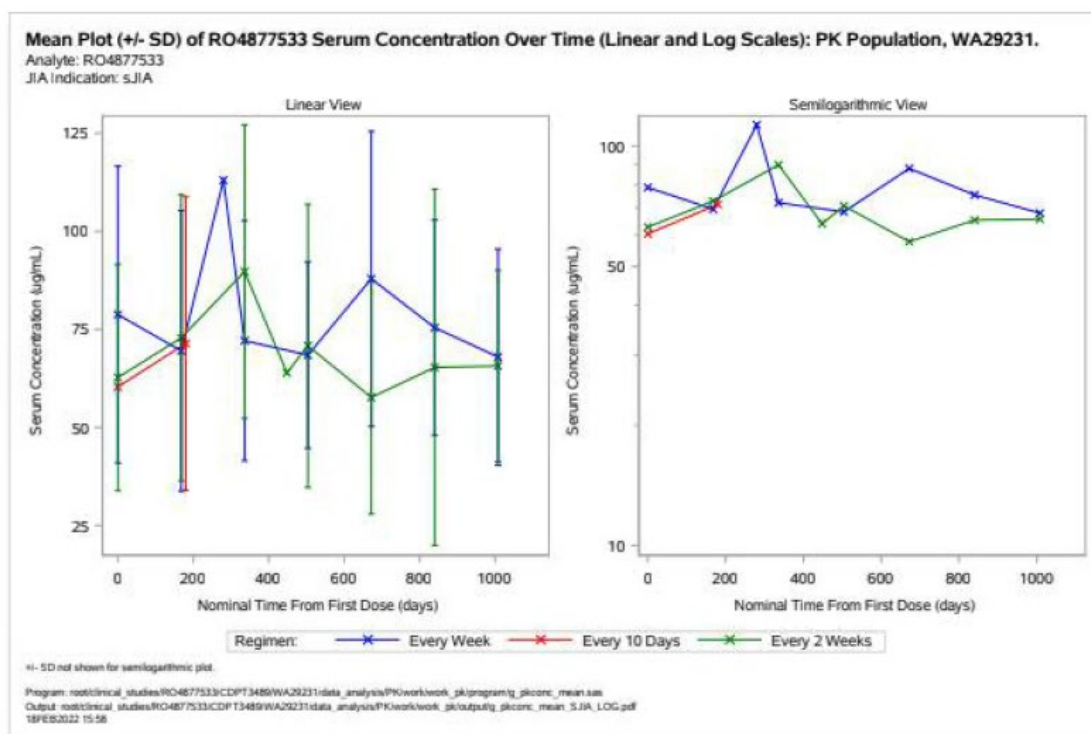


Figure 4 Mean TCZ Serum Concentrations vs Time in sJIA in Study WA29231 (Linear and Log)

CHMP comment

Based on the data provided, it is agreed that long-term trough exposures in Study WA29231 were maintained within the expected range of exposures in patients with pJIA and sJIA following multiple SC TCZ administrations at pre-defined dosing regimens, per disease and bodyweight category. External validation by pop PK would have been useful to comprehensively assess the long-term PK data.

Immunogenicity

pJIA

A total of 41/44 patients were classified as post-baseline evaluable. Of the 3 patients who were not post-baseline evaluable, one patient did not have a baseline sample collected.

Two patients (one in the <30 kg BW group and one in the ≥30 kg BW group) were ADA positive at the LTE study baseline visit (and both were also positive for treatment-induced ADA during the core study period) but neither was ADA positive post-baseline during the LTE study. Of the 41 post-baseline evaluable patients, there were no treatment-induced ADA reported in the <30 kg BW group. However, there were two patients in the ≥30 kg BW group who presented with treatment-induced ADAs; both patients developed ADA of neutralizing potential and neither developed ADAs of the IgE isotype.

One patient had two post baseline ADA samples with a positive confirmatory assay and confirmed neutralizing potential, at Week 48 and Week 72, but had no impact on the PK profile. The patient did not experience any hypersensitivity reactions (excluding ISRs) or ISRs and completed the study.

The other patient had one positive confirmatory assay result at Week 48 (Day 337), with confirmed neutralizing potential. In this patient, TCZ concentration at baseline was slightly higher than the median Ctrough reported in the Q2W dosing group (12.5 µg/mL vs 8.09 µg/mL). Exposure values at Week 24 and Week 48 (1.13 µg/mL and 3.33 µg/mL, respectively) were below the observed median concentration (8.79 µg/mL and 7.87 µg/mL, respectively). It should be noted though that the TCZ concentration at Week 24 of the patient was excluded from the analysis due to compliance issues. A direct impact of ADAs on TCZ exposure is therefore difficult to assess, but cannot be fully excluded.

This patient did not experience any hypersensitivity reactions but did experience several ISRs (injection site erythema, injection site haematoma, injection site swelling, and injection site pruritus) – all ISRs were non-serious CTCAE Grade 1 events considered related to TCZ treatment by the investigator, did not lead to study treatment interruption, and resolved without sequelae. The patient was discontinued on Day 452 (Week 64) for lack of efficacy.

The figure below shows the spread of Ctrough values with a highlight of the three post-baseline samples (red dots) with concomitant neutralizing ADAs.

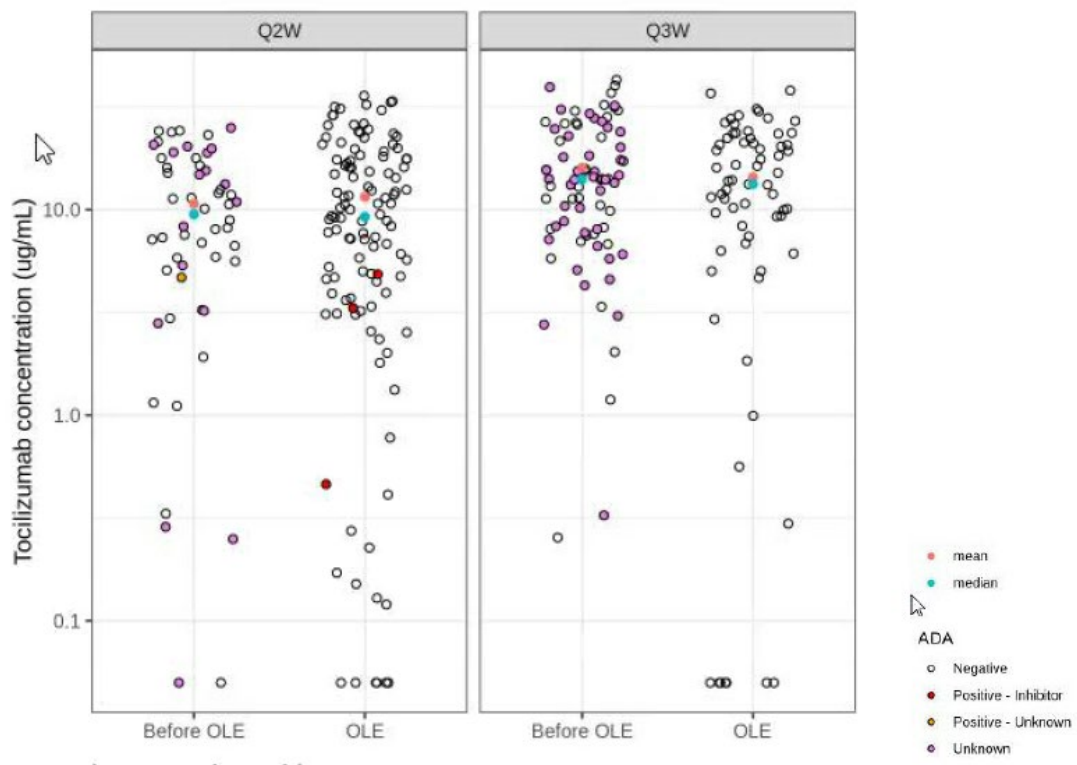


Figure 5 Distribution of Ctrough in pJIA patients in Study WA28118 (before OLE) and WA29231 (OLE) (Semi-Log), with associated ADAs status

sJIA

A total of 37/38 sJIA patients were classified as post-baseline evaluable. Of these 37 patients, none developed ADA against TCZ during the study period.

CHMP comment

A certain potential for reduced efficacy in connection with ADA-development is indicated by immunogenicity results in pJIA patients. The overall immunogenicity seems to be at the expected range, however, the sample size is limited.

Pharmacodynamics and PK/PD**pJIA**Soluble IL-6 Receptor (sIL-6R)

In pJIA patients, sIL-6R levels did not fluctuate significantly over the time course of the study, going from a median (range) value of 566.00 (22.20-976.00) ng/mL at baseline to 501.00 (39.3-908.00) ng/mL at Week 144. sIL-6R levels were slightly higher in the Q3W dosing regimen group as compared to Q2W, consistent with previous observations in Study WA28117.

Interleukin-6 (IL-6)

In pJIA patients, median (range) IL-6 levels were steady over time, going from 21.00 (3.12-422.00) pg/mL at baseline to 19.40 (3.12-140.00) pg/mL at Week 144. Similar to sIL6R, IL-6 values were higher in the Q3W dosing regimen group as compared to Q2W, as observed previously in Study WA28117.

Overall, in pJIA patients, both sIL-6R and IL-6 levels did not significantly vary during the time course of the study.

sJIASoluble IL-6 Receptor (sIL-6R)

Similarly, in sJIA patients, sIL-6R levels did not significantly vary over time. sIL6R median (range) values were measured at 658.00 (48.90-1490.00) ng/mL at baseline and 728 (455.0-872.0) ng/mL at Week 144. sIL-6R levels were slightly higher in the Q2W/Q10D dosing regimen group as compared to QW, consistent with previous observations in Study WA28118.

Interleukin-6 (IL-6)

In Study WA29231, sIL-6R levels measured in sJIA patients did not fluctuate significantly over time. IL-6 levels slightly decreased from baseline to Week 144, with a larger between-subject variability and a reduction in the sample size observed over time.

Overall, in sJIA patients, both sIL-6R and IL-6 levels did not significantly vary during the time course of the study.

PK/PD

Exploratory PK analyses showed that trough exposures over time in this LTE study were maintained within the range of exposures expected to provide a clinical benefit in patients with pJIA and sJIA, and exploratory analyses showed that levels for PD parameters evaluated (sIL-6R, IL-6, ESR and CRP, see clinical efficacy) remained stable over the course of the study.

CHMP comment

PD data indicate a modest variability in PD marker sIL-6R and IL-6 that seems to be slightly reduced at week 144 but increased (IL-6) in sJIA subjects. Mean values of sIL-6R was reduced in pJIA but increased in sJIA patients. Overall it is agreed that in both indications, both sIL-6R and IL-6 level variability during the time course of the study is not indicated to be clinically significant. See Section 2.3.3 clinical efficacy for ESR and CRP data.

2.3.3. Clinical study**Study WA29231 Long-Term Extension Study to Evaluate the Safety and Efficacy of Subcutaneous Tocilizumab in Patients With Polyarticular-Course and Systemic Juvenile Idiopathic Arthritis"****Description****Methods*****Study participants***

Patients diagnosed with pJIA or sJIA according to ILAR classification (Petty et al. 2004) who have completed treatment and had an adequate response to TCZ SC in the JIGSAW studies (Study WA28117 in patients with pJIA and Study WA28118 in patients with sJIA). Patients who withdraw from this LTE study for any reason will not be allowed to re-enrol. Patients entering the JIGSAW LTE study had previously completed 1year of SC TCZ treatment in the applicable core JIGSAW study.

Prior discontinuation of SC TCZ because of inadequate clinical response during participation in a JIGSAW study and poorly controlled disease (in opinion of treating physician) despite treatment with SC were exclusion criteria. Further patients who discontinued IV TCZ because of inadequate clinical response or safety reasons were also excluded from the study.

CHMP comment

Patients were rolled over from the two core studies i.e. Study WA28117 in patients with pJIA and Study WA28118 in patients with sJIA to support the use of TCZ SC in the two indications. The studies were assessed previously.

Treatments

Patients received 162 mg SC TCZ according to body weight (BW) and JIA subtype.

JIA Subtype	Dosing Frequency (162 mg SC TCZ)	
	< 30 kg	≥ 30 kg
pJIA	Every 3 weeks	Every 2 weeks
sJIA	Every 2 weeks ^a	Every week

JIA=juvenile idiopathic arthritis; pJIA=polyarticular-course juvenile idiopathic arthritis; SC=subcutaneous; sJIA=systemic juvenile idiopathic arthritis; TCZ=tocilizumab.
^a Dosing regimen following review of Study WA28118 interim analysis data. The initial dosing regimen was every 10 days.

Batch numbers: 1146283, 1149394, 1151097, 1152959, 1154226, 1156203, 1157296, 1159652, 1161659, 1162287, 1162965, 1166231, 1168296

CHMP comment

Treatment is (after interims analysis of Study WA28118) according the authorised posology.

Objective(s) / Outcomes/endpoints

Objectives	Endpoints
<p>Safety</p> <ul style="list-style-type: none"> To evaluate the long-term safety of SC administration of TCZ in patients with pJIA and sJIA for up to 5 years 	<ul style="list-style-type: none"> Incidence of adverse events (AEs, including local injection-site reactions) and serious AEs (SAEs) Incidence and severity of adverse events of special interest (AESI) The patient-year rates for AE, SAE, AESI and selected AEs Incidence and severity of clinical laboratory abnormalities
<p>Efficacy</p> <ul style="list-style-type: none"> To describe the long-term efficacy of SC TCZ in patients with pJIA and sJIA for up to 3 years. 	<ul style="list-style-type: none"> Absolute and change from baseline in Juvenile Arthritis Disease Activity Score (JADAS)-71 Proportion of patients with inactive disease and clinical remission Absolute and change from baseline in Childhood Health Assessment Questionnaire (CHAQ)

Objectives	Endpoints
<ul style="list-style-type: none"> To assess long-term pharmacodynamics of SC TCZ in patients with pJIA and sJIA for up to 3 years 	<ul style="list-style-type: none"> Absolute and change from baseline in serum IL-6 and sIL-6R levels, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) Incidence of anti-TCZ antibodies
<ul style="list-style-type: none"> To assess long-term pharmacokinetics of SC TCZ in patients with pJIA and sJIA for up to 3 years 	<ul style="list-style-type: none"> Serum TCZ concentration and/or population PK model-predicted PK exposures (area under the concentration-time curve [AUC], maximum and minimum plasma concentration [C_{max} and C_{min}]) for the different dosing regimens at steady state.

Sample size

The maximum sample size is determined by the number of patients with JIA enrolled in and successfully completing the JIGSAW studies

Randomisation and blinding (masking)

N/A

Statistical Methods

All statistical analyses are descriptive in nature

Study population

For the analyses, the following populations were defined:

- Safety Population: included all patients who received at least one dose of SC TCZ and who had at least one post dose assessment in this LTE study.
- ITT (intent to treat): included all patients enrolled who received at least one dose of SC TCZ in this LTE study.
- PK (Pharmacokinetic)-evaluable: included all patients who received at least one dose of SC TCZ and who had at least one post dose PK assessment in this LTE study.

Results

Participant flow

pJIA

Forty-six pJIA patients completed Study WA28117, of which a total of 44 patients were enrolled in LTE Study WA29231 across 21 sites in 11 countries:

A total of 19 patients (43.2%) completed the study, 13 patients (54.2%) in the < 30 kg BW group and 6 patients (30.0%) in the \geq 30 kg BW group.

Of the 25 patients discontinued from the study, 2 patients (4.5%) discontinued due to an AE; 1 patient each from the < 30 kg BW group and \geq 30 kg BW group (4.2% vs 5.0%).

The remaining 23 patients (52.3%) discontinued from the study for non-safety reasons. The majority of non-safety reasons for study discontinuation were (in the < 30 kg BW group and \geq 30 kg BW group, respectively):

- Other: 3 patients (12.5%) and 5 patients (25.0%). These 8 patients discontinued the study so that they could transition to commercially available TCZ in their country/region, as per protocol.
- Withdrawal by subject: 1 patient (4.2%) and 4 patients (20.0%)
- Lack of efficacy: 2 patients (8.3%) and 2 patients (10.0%)
- Study terminated by sponsor: 3 patients (12.5%) in the < 30 kg BW group.)

sJIA

Forty-four sJIA patients completed Study WA28118, of which 38 patients were enrolled in the LTE study across 22 sites.

In total, 6 patients (15.8%) completed the study, 1 patient (5.3%) in the < 30 kg BW group and 5 patients (26.3%) in the ≥ 30 kg BW group.

Overall, 32 patients (84.2%) were discontinued from the study; however, none of the discontinuations were for safety reasons.

The majority of non-safety reasons for study discontinuation were (in the < 30 kg BW group and ≥ 30 kg BW group, respectively):

- Other: 8 patients (42.1%) and 8 patients (42.1%). These 16 patient discontinued the study so that they could transition to commercially available TCZ in their country/region, as per protocol.
- Withdrawal by subject: 2 patients (10.5%) and 4 patients (21.1%)
- Study terminated by sponsor: 4 patients (21.1%) in the < 30 kg BW group.
- Physician decision: 2 patients (10.5%) and 2 patients (10.5%).

CHMP comment

The study was terminated by the sponsor 1 year earlier than planned due to operational reasons.

Dosing regimen change

pJIA

Of the 24 patients in the < 30 kg BW group, 17 patients switched dosing regimen over the course of the study after their BW stably increased to ≥ 30 kg. These 17 patients were initially on a Q3W dosing regimen and switched to the Q2W dosing regimen.

sJIA

Of the 19 patients in < 30 kg BW group, 11 patients switched dosing regimen over the course of the study after their BW stably increased to ≥ 30 kg. These 11 patients were initially on a Q10D or Q2W dosing regimen and switched to the QW dosing regimen.

Five patients started the study on a Q10D dosing regimen, and subsequently switched to different dosing regimens (2 patients initially on the Q10D dosing regimen switched to Q2W; and 3 patients initially on the Q10D dosing regimen switched to Q2W and the subsequently to QW after their BW stably increased to ≥ 30 kg).

Recruitment

Patients entering the JIGSAW LTE study had previously completed 1 year of SC TCZ treatment in the applicable core JIGSAW study.

Individual participation in the JIGSAW LTE study continued until commercial availability of SC TCZ or for a maximum of 5 years.

Study WA29231 began (i.e. First patient First Visit [FPFV]) on 16 July 2014 and the study was completed (i.e. last patient last visit [LPLV]) on 24 November 2021.

The study was terminated by the Sponsor approximately 1 year earlier than planned due to operational reasons. At the time of study termination, there were only 7 patients ongoing in the study, all within the final year of study participation. All 7 patients were able to continue their TCZ treatment following study termination either by transfer to a post-trial access scheme (treatment provided until 5 years' post-baseline of JIGSAW LTE study) or by switching to use of commercial TCZ.

Baseline data

pJIA

Overall, the majority of patients were female (72.7%), white (88.6%) and of non-Hispanic or Latino ethnicity (70.5%). The two BW groups (< 30 kg and \geq 30 kg) differed in median age (7.0 years vs. 15.5 years), median height (122.0 cm vs. 165.4 cm), and median weight (24.5 kg vs. 59.1 kg).

sJIA

Overall, approximately half of the patients were female (55.3%) and the majority were white (84.2%) and of non-Hispanic or Latino ethnicity (78.9%). The two BW groups (< 30 kg and \geq 30 kg) differed in median age (4.0 years vs. 14.0 years), median height (103.6 cm vs. 154.8 cm), and median weight (18.4 kg vs. 46.5 kg).

Baseline disease characteristic

pJIA

The proportion of patients on background oral corticosteroids at baseline were 33.3% within the < 30 kg BW group and 45.0% within \geq 30 kg BW group. The previous use of a non-biologic DMARD was 95.8% for patients within < 30 kg BW group and 100.0% for patients within the \geq 30 kg BW group.

The median JADAS-71 scores at baseline for the < 30 kg BW group and the \geq 30 kg BW group were 0.40 and 2.05, respectively, with a median of 0 (mean 0.5) active joints at baseline in the < 30 kg BW group, and a median of 0 (mean 2.7) active joints at baseline in the \geq 30 kg BW group.

sJIA

The proportion of patients on background oral corticosteroids at baseline were 31.6% within the < 30 kg BW group and 26.3% within \geq 30 kg BW group. The previous use of a non-biologic DMARD was 57.9% for patients within < 30 kg and 94.7% for patients within the \geq 30 kg BW group.

The median JADAS-71 scores at baseline for the < 30 kg BW group and the \geq 30 kg BW group were 0.40 and 0.25, respectively, with a median of 0 (mean 0.3) active joints at baseline in the < 30 kg BW group, and a median of 0 (mean 0.5) active joints at baseline in the \geq 30 kg BW group.

CHMP comment

Previous use of a biologic DMARD was 100.0% in all patients groups, since all patients had received TCZ in the JIGSAW core studies prior to enrolling in this LTE study.

Number analysed

pJIA

All 44 patients received at least one dose of study treatment. Of these, 4 patients (9.1%) completed all dose administrations. The median number of doses was 93.0 in the < 30 kg BW group and 106.5 in the \geq 30 kg BW group.

sJIA

All 38 patients received at least one dose of study treatment. Of these, 3 patients (7.9%) completed all dose administrations. The median number of doses was 90.0 in the < 30 kg BW group and 183.0 in the \geq 30 kg BW group

The difference in the median number of doses between the two body weight groups was due the different dose frequencies.

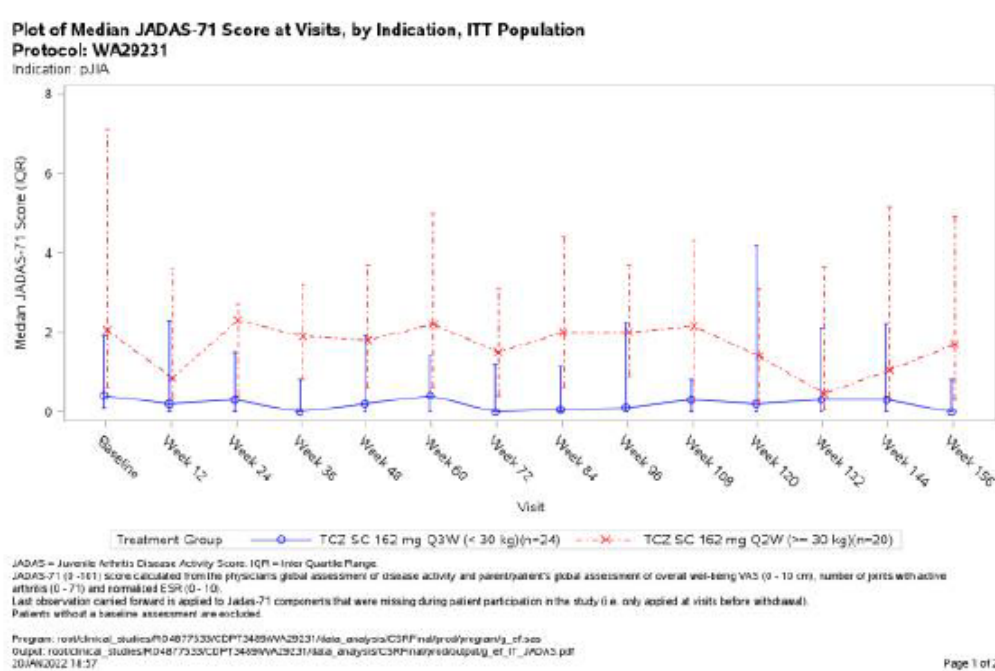
Efficacy results

Juvenile arthritis disease activity score (JADAS)-71

pJIA

Both BW groups had low median JADAS-71 scores at baseline (0.4 for patients weighing < 30 kg and 2.05 for patients weighing \geq 30 kg) (Figure 2). The median JADAS-71 score remained stable over the course of the study; change from baseline was - 0.20 for patients weighing < 30 kg and \geq 0.50 for patients weighing \geq 30 kg at Week 156.

Figure 2 Median JADAS-71 Score at Visits by Indication, ITT Population (pJIA Indication)

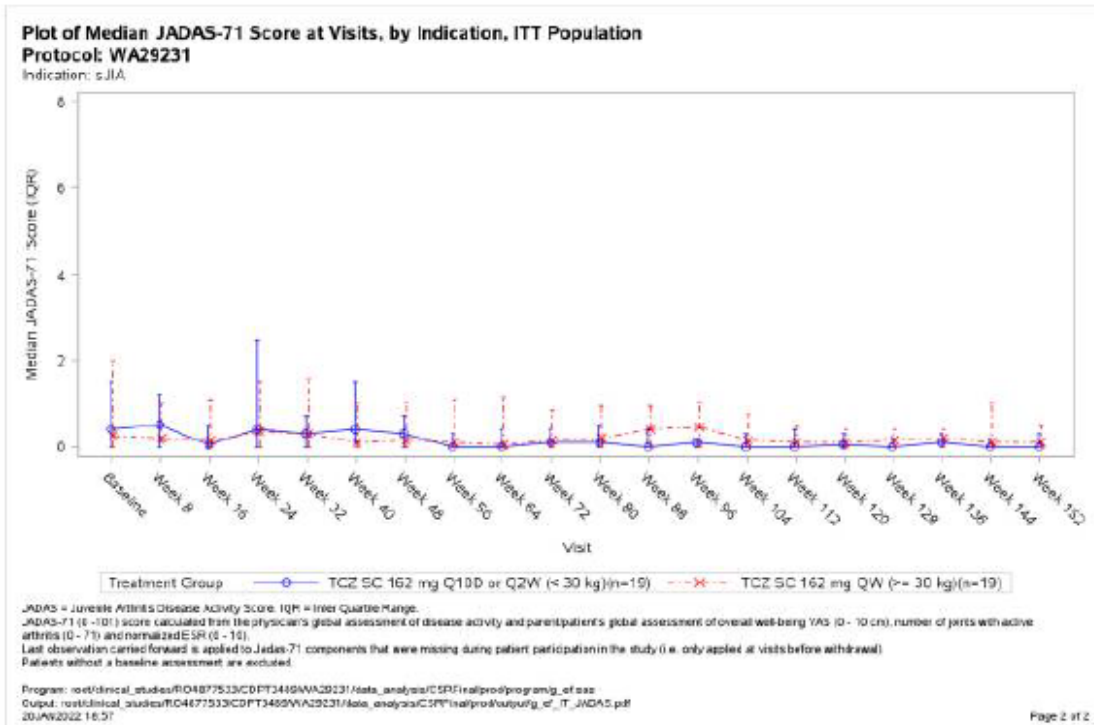


sJIA

Both BW groups had low median JADAS-71 scores at baseline (0.4 for patients weighing < 30 kg and 0.25 for patients weighing \geq 30 kg).

The median JADAS-71 score remained stable over the course of the study; change from baseline was - 0.10 for patients weighing < 30 kg and patients weighing \geq 30 kg at Week 152.

Figure 3 Median JADAS-71 Score at Visits by Indication, ITT Population (sJIA Indication)



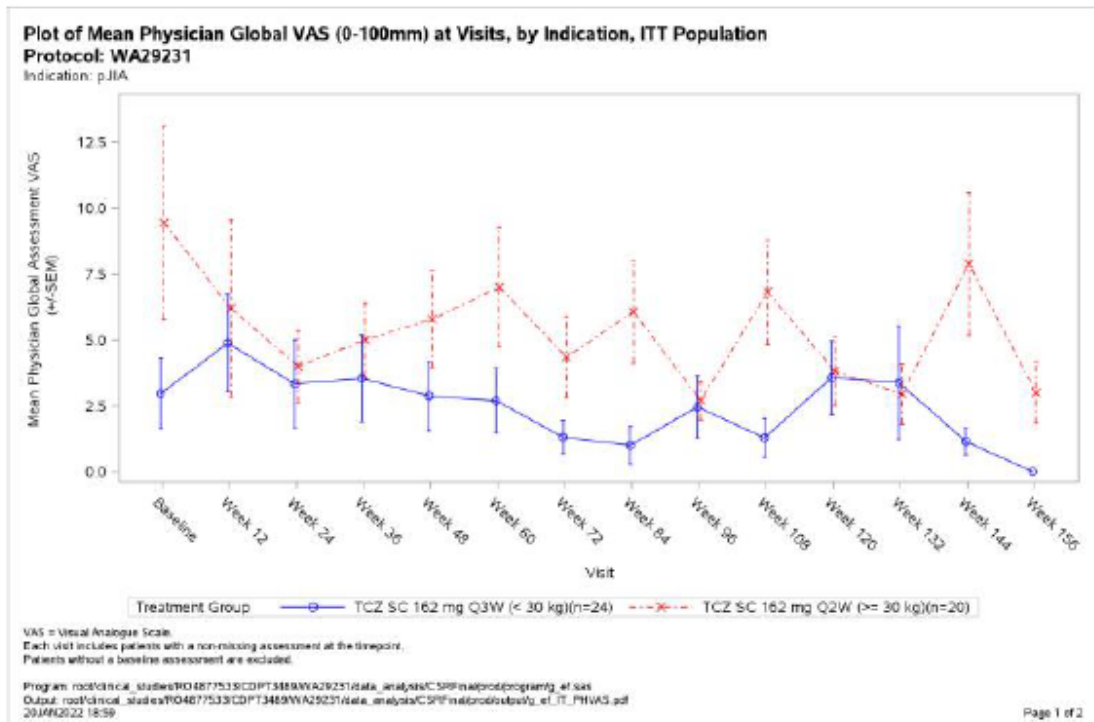
JADAS-71 components

Physician global assessment VAS

pJIA

Both BW groups had low mean physician global assessment VAS at baseline. The mean VAS remained consistently low over the course of the study (Figure 4).

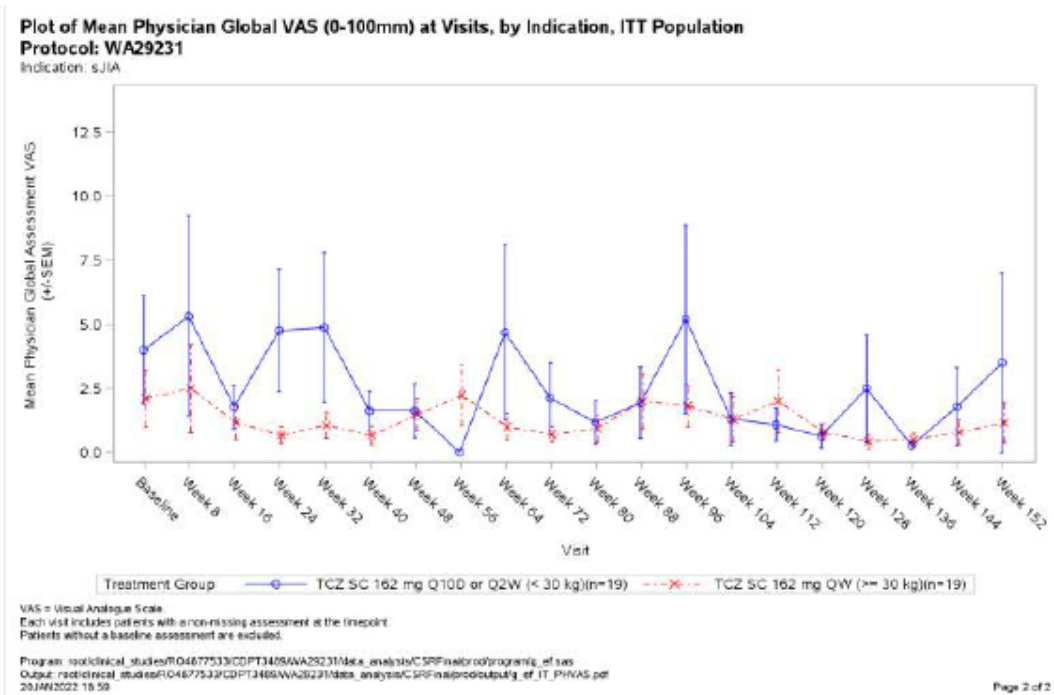
Figure 4 Physician Global Assessment VAS (0-100 mm) at Visits by Indication, ITT Population (pJIA Indication)



sJIA

Both BW groups had low mean physician global assessment VAS at baseline. The mean VAS remained consistently low over the course of the study (Figure 5).

Figure 5 Physician Global Assessment VAS (0-100 mm) at Visits by Indication, ITT Population (sJIA Indication)

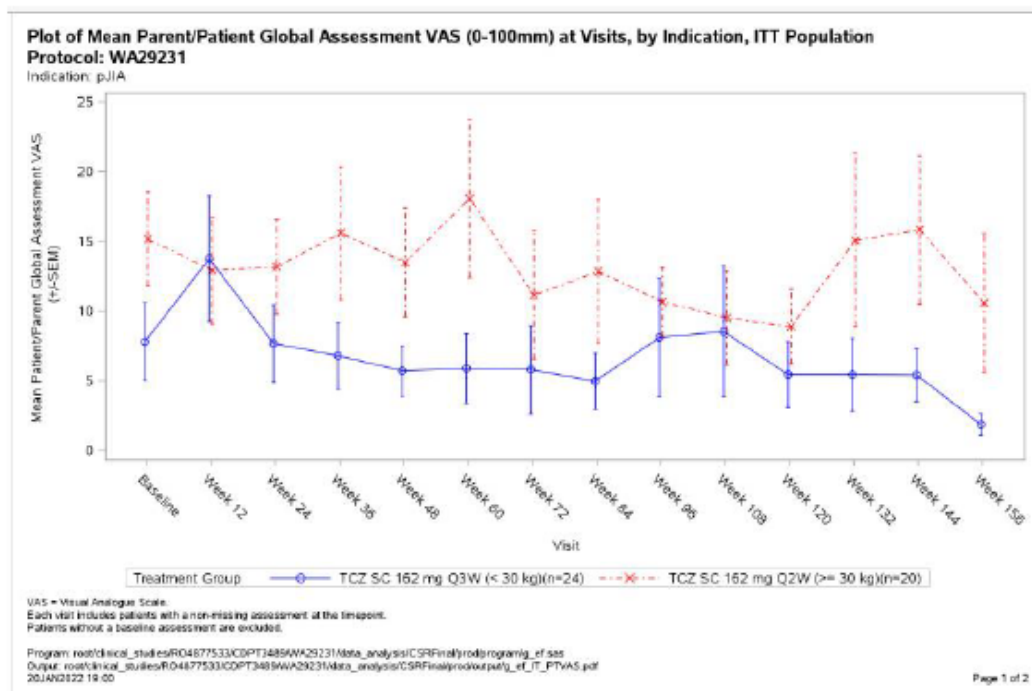


Patient/parent global assessment VAS

pJIA

Both BW groups had low mean patient's (parent's/guardian's) global assessment VAS at baseline. At Week 156, the mean VAS changed from 7.8 mm (baseline) to 1.8 mm and from 15.2 mm (baseline) to 10.6 mm for the < 30 kg and \geq 30 kg BW groups, respectively. The mean VAS absolute values remained consistently low over the course of the study for both the < 30 kg BW group and the \geq 30 kg BW group (Figure 6).

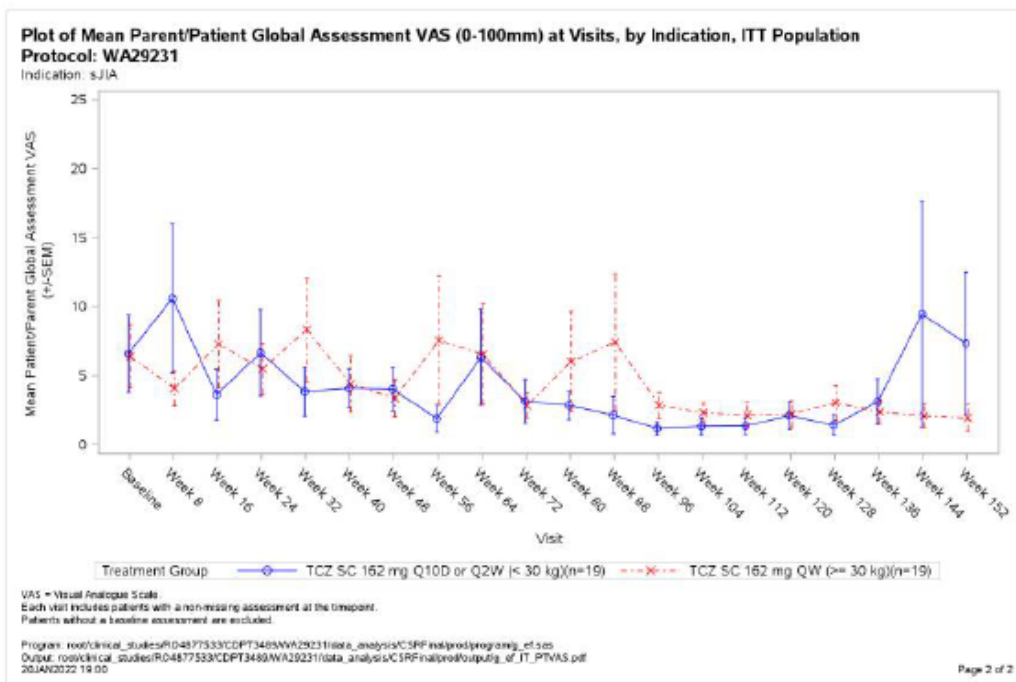
Figure 6 Parent/Patient Global Assessment VAS (0-100mm) at Visits by Indication, ITT Population (pJIA Indication)



sJIA

Both BW groups had low mean patient's (parent's/guardian's) global assessment VAS at baseline. The mean VAS absolute values remained consistently low over the course of the study for both the < 30 kg and \geq 30 kg BW groups. (Figure 7).

Figure 7 Parent/Patient Global Assessment VAS (0-100mm) at Visits by Indication, ITT Population (sJIA Indication)



Number of active joints

pJIA

Patients had low mean active joint numbers at baseline and these remained low in the < 30 kg BW group (0.5 at baseline vs. 0.1 at Week 156) and the \geq 30 kg BW group (2.7 at baseline vs. 1.1 at Week 156).

sJIA

Patients had low mean active joint numbers at baseline and these remained low in the < 30 kg BW group (0.3 at baseline vs 0.3 at Week 152) and the \geq 30 kg BW group (0.5 at baseline vs 0.1 at Week 152).

Erythrocyte sedimentation rate (ESR)

pJIA

Overall, patients had a low mean ESR at baseline in both the < 30 kg and the \geq 30 kg BW group and were maintained at similar levels throughout the study until Week 156.

In patients of <30 kg BW group, the mean ESR decreased from 3.55 mm/hr at baseline to 2.63 mm/hr at Week 156. In the \geq 30 kg BW group, the mean ESR decreased from 4.55 mm/hr at baseline to 3.08 mm/hr at Week 156. The peak observed at Week 84 in the < 30 kg BW group was due to an outlier (1 patient who had an ESR value of 118 mm/hr at Week 84).

sJIA

The patients had a low mean ESR at baseline in both the < 30 kg and the \geq 30 kg BW group and were maintained at similar levels throughout the study until Week 152.

In patients of < 30 kg BW group, the mean ESR decreased from 5.89 mm/hr at baseline to 3.56 mm/hr at Week 152. In the \geq 30 kg BW group, the mean ESR was 2.50 mm/hr at baseline, which was

maintained at 2.50 mm/hr at Week 152. The peak observed at Week 24 in the < 30 kg BW group was due to an outlier (1 patient had an ESR of 80 mm/hr at Week 24).

C-reaction protein (CRP)

pJIA

Mean CRP levels were low at baseline and remained low over the course of the study with some minor fluctuations in both BW groups.

sJIA

Mean CRP levels were low at baseline and remained low over the course of the study with some minor fluctuations in both BW groups. No patient experienced CRP values outside of the normal range during the course of the study.

Inactive disease

pJIA

In the < 30 kg BW group, there was a small increase in the proportion of patients who had inactive disease over the course of the study. The proportion of patients with inactive disease in the \geq 30 kg BW group was lower compared to the < 30 kg BW group, and remained stable between baseline and at Week 156.

sJIA

In general, a slightly increasing proportion of patients had inactive disease over the course of the study, irrespective of BW group.

Table 17 Proportion of patients with Inactive Disease at Visits by Indication, ITT Population

Visit	Proportion of patients with Inactive Disease			
	pJIA (N=44)		sJIA (N=38)	
	< 30 kg (n=24)	\geq 30 kg (n=20)	< 30 kg (n=19)	\geq 30 kg (n=19)
Baseline	18/24 (75.0%)	10/20 (50.0%)	14/19 (73.7%)	15/19 (78.9%)
Week 48	18/23 (78.3%)	8/19 (42.1%)	16/17 (94.1%)	15/17 (88.2%)
Week 72	16/23 (69.6%)	9/17 (52.9%)	14/17 (82.4%)	15/17 (88.2%)
Week 96	17/22 (77.3%)	10/17 (58.8%)	13/15 (86.7%)	13/17 (76.5%)
Week 120	17/21 (81.0%)	7/16 (43.8%)	10/12 (83.3%)	14/16 (87.5%)
Week 156/ 152*	17/19 (89.5%)	8/15 (53.3%)	10/11 (90.9%)	12/13 (92.3%)

* Week 156 for patients with pJIA and Week 152 for patients with sJIA.

Source: t_ef_prop_ITT_INACT

Clinical remission

pJIA

The proportion of patients in clinical remission remained relatively stable over the course of the study in both BW groups. Overall, 19 patients (55.9%) achieved clinical remission at Week 156; 14 patients (73.7%) in < 30 kg BW group and 5 patients (33.3%) in \geq 30 kg BW group.

sJIA

The proportion of patients in clinical remission remained relatively stable over the course of the study in both BW groups. Overall, 19 patients (79.2%) achieved clinical remission at Week 152; 9 patients (81.8%) in < 30 kg BW group and 10 patients (76.9%) in \geq 30 kg BW group.

Table 18 Proportion of patients in Clinical Remission at Visits by Indication, ITT Population

Visit	Proportion of patients in Clinical Remission			
	pJIA (N=44)		sJIA (N=38)	
	< 30 kg (n=24)	≥ 30 kg (n=20)	< 30 kg (n=19)	≥ 30 kg (n=19)
Week 24	12/24 (50.0%)	8/19 (42.1%)	12/17 (70.6%)	13/19 (68.4%)
Week 48	12/23 (52.2%)	4/19 (21.1%)	10/17 (58.8%)	13/17 (76.5%)
Week 72	14/23 (60.9%)	7/17 (41.2%)	13/17 (76.5%)	13/17 (76.5%)
Week 96	13/22 (59.1%)	6/17 (35.3%)	10/15 (66.7%)	14/17 (82.4%)
Week 120	13/21 (61.9%)	5/16 (31.3%)	10/12 (83.3%)	10/16 (62.5%)
Week 156/ 152*	14/19 (73.7%)	5/15 (33.3%)	9/11 (81.8%)	10/13 (76.9%)

* Week 156 for patients with pJIA and Week 152 for patients with sJIA.

Source: t_wf_prop_ITT_RMES

Pain VAS

pJIA

The mean pain VAS remained consistently low over the course of the study (Figure 10).

sJIA

The mean pain VAS remained consistently low over the course of the study. The apparent peak at Week 144 and 156 in the < 30 kg BW group was due to one single patient who had several episodes of increase in pain throughout the study. Due to then lower patient numbers still left in the study at that time, a minor impact on the mean is observable.

Childhood health assessment questionnaire-disability index (CHAQ-DI)

pJIA

CHAQ-DI scores were low at baseline and remained stable over the course of the study in both BW groups. Change from baseline in mean CHAQ-DI scores (\pm SD) to Week 156 was -0.06 ± 0.188 for patients weighing < 30 kg and -0.06 ± 0.084 for patients weighing ≥ 30 kg at Week 156.

sJIA

CHAQ-DI scores were low at baseline and remained stable over the course of the study in both BW groups. Change from baseline in mean CHAQ-DI scores (\pm SD) to Week 152 was patient 0.02 ± 0.339 for patients weighing < 30 kg and -0.06 ± 0.141 for patients weighing ≥ 30 kg at Week.

Safety results

Adverse events

All patients experienced at least one AE over the course of the study.

pJIA

All 44 patients (100.0%) experienced at least one AE (any grade) during the study. The most frequent AEs by SOC ($\geq 30\%$ of patients in either BW group) were (< 30 kg BW group and ≥ 30 kg BW group, respectively):

- Infections and infestations (24 patients [100.0%] and 18 patients [90.0%]);
- Musculoskeletal and connective tissue disorders (15 patients [62.5%] and 14 patients [70.0%]);
- Gastrointestinal disorders (14 patients [58.3%] and 11 patients [55.0%]);

- Respiratory, thoracic and mediastinal disorders (14 patients [58.3%] and 8 patients [40.0%]);
- General disorders and administration site conditions (11 patients [45.8%] and 10 patients [50.0%]);
- Injury, poisoning and procedural complications (13 patients [54.2%] and 7 patients [35.0%]);
- Skin and subcutaneous tissue disorders (13 patients [54.2%] and 5 patients [25.0%]);
- Nervous system disorders (7 patients [29.2%] and 7 patients [35.0%])

The most frequent AEs by PT ($\geq 20\%$ of patients in either BW group) were (< 30 kg BW group and ≥ 30 kg BW group, respectively):

- Arthralgia (11 patients [45.8%] and 5 patients [25.0%]);
- Gastroenteritis (11 patients [45.8%] and 3 patients [15.0%]);
- Nasopharyngitis (10 patients [41.7%] and 9 patients [45.0%]);
- Diarrhoea (10 patients [41.7%] and 3 patients [15.0%]);
- Vomiting (10 patients [41.7%] and 2 patients [10.0%]);
- Cough (10 patients [41.7%] and 2 patients [10.0%]);
- Pyrexia (7 patients [29.2%] and 3 patients [15.0%]);
- Neutropenia (6 patients [25.0%] and 1 patient [5.0%]);
- Headache (4 patients [16.7%] and 6 patients [30.0%]);
- Juvenile idiopathic arthritis (3 patients [12.5%] and 4 patients [20.0%]);
- Oropharyngeal pain (3 patients [12.5%] and 6 patients [30.0%]);
- Injection site erythema (2 patients [8.3%] and 4 patients [20.0%]);
- Nausea (1 patient [4.2%] and 4 patients [20.0%]);
- Tonsillitis (1 patient [4.2%] and 5 patients [25.0%]);

sJIA

All 38 patients (100.0%) experienced at least one AE (any grade) during the study. The most frequent AEs by SOC ($\geq 30\%$ of patients in either BW group) were (< 30 kg BW group and ≥ 30 kg BW group, respectively):

- Infections and infestations (18 patients [94.7%] and 15 patients [78.9%]);
- Gastrointestinal disorders (11 patients [57.9%] and 8 patients [42.1%]);
- Musculoskeletal and connective tissue disorders (10 patients [52.6%] and 9 patients [47.4%]);
- Injury, poisoning and procedural complications (10 patients [52.6%] and 7 patients [36.8%]);
- Respiratory, thoracic and mediastinal disorders (9 patients [47.4%] and 8 patients [42.1%]);
- General disorders and administration site conditions (9 patients [47.4%] and 7 patients [36.8%]);
- Skin and subcutaneous tissue disorders (6 patients [31.6%] and 8 patients [42.1%]);

The most frequent AEs by PT ($\geq 20\%$ of patients in either BW group) were (< 30 kg BW group and ≥ 30 kg BW group, respectively):

- Nasopharyngitis (5 patients [26.3%] and 10 patients [52.6%]);
- Upper respiratory tract infection (9 patients [47.4%] and 4 patients [21.1%]);
- Arthralgia (5 patients [26.3%] and 5 patients [26.3%]);
- Cough (7 patients [36.8%] and 2 patients [10.5%]);
- Oropharyngeal pain (3 patients [15.8%] and 5 patients, 26.3%);
- Pyrexia (7 patients [36.8%] and 3 patients [15.8%]);
- Rash (4 patients [21.1%] and 4 patients [21.1%]);
- Headache (5 patients [26.3%] and 3 patients [15.8%]);
- Diarrhoea (4 patients [21.1%] and 3 patients [15.8%]);
- Ear infection (5 patients [26.3%] and 2 patients [10.5%]);
- Vomiting (6 patients [31.6%] and 1 patient [5.3%]);
- Sinusitis (0 and 4 patients [21.1%]);

Adverse events related to treatment

pJIA

Of the 44 patients, 29 patients (65.9%) experienced AEs that were considered related to SC TCZ treatment by the Investigator (< 30 kg BW group: 17 patients [70.8%] and ≥ 30 kg BW group: 12 patients [60.0%]).

The overall AE rate was 126.0 events per 100 PY across both BW groups ([95% CI: 109.84, 143.90]).

All related AEs were assessed as non-serious, with the exception of one SAE of pneumonia (Grade 3) in one patient in the < 30 kg BW group. The patient did not have to interrupt study treatment and recovered without sequelae.

sJIA

Of the 38 patients, 24 patients (63.2%) experienced AEs that were considered related to SC TCZ treatment by the Investigator (< 30 kg BW group: 13 patients [68.4%] and ≥ 30 kg BW group: 11 patients [57.9%]).

The overall AE rate was 69.3 events per 100 PY across both BW groups ([95% CI: 55.49, 85.46]).

Of these 24 patients, 6 patients (15.8%) had related AEs that led to dose modification/interruption. No related AEs led to withdrawal from study treatment.

All related AEs were assessed as non-serious, with the exception of two SAEs (alanine aminotransferase increased [Grade 3] and aspartate aminotransferase increased [Grade 2] with the same onset date) experienced by one patient in the < 30 kg BW group. The patient did not have to interrupt study treatment (but concomitantly used methotrexate was interrupted) and recovered without sequelae.

Adverse events by intensity

pJIA

Table 5 Summary of AEs by Highest NCI CTCAE Grade, pJIA Indication, Safety Population

Grade	<30kg (N=24)	≥30kg (N=20)	All Patients (N=44)
Any Grade	24 (100%)	20 (100%)	44 (100%)
Grade 1	4 (16.7%)	2 (10.0%)	6 (13.6%)
Grade 2	11 (45.8%)	13 (65.0%)	24 (54.5%)
Grade 3	8 (33.3%)	5 (25.0%)	13 (29.5%)
Grade 4	1 (4.2%)	0	1 (2.3%)

A total of 13 patients (29.5%) experienced a Grade 3 AE and 1 patient experienced a Grade 4 AE. There were no Grade 5 (fatal) AEs reported.

The most common Grade 3 AEs by SOC ($\geq 5\%$ of all pJIA patients) were Infections and infestations (3 patients; 6.8%), Injury, poisoning and procedural complications (3 patients; 6.8%), and Blood and lymphatic system disorders (3 patients; 6.8%). The most common Grade 3 AEs by PT that were reported in >1 patient were Neutrophil count decreased (2 patients) and Neutropenia (3 patients).

The PT of the Grade 4 AE was Neutropenia. The AE was non-serious and considered related to study treatment by the investigator. The patient was withdrawn from TCZ treatment and subsequently discontinued from the study. The AE resolved without sequelae, and the patient did not experience any infection and infestation AEs within 30 days of the Grade 4 neutropenia event

sJIA

Table 6 Summary of AEs by NCI CTCAE Grade, sJIA Indication, Safety Population

Grade	<30kg (N=19)	≥30kg (N=19)	All Patients (N=38)
Any Grade	19 (100%)	19 (100%)	38 (100%)
Grade 1	4 (21.1%)	11 (57.9%)	15 (39.5%)
Grade 2	8 (42.1%)	4 (21.1%)	12 (31.6%)
Grade 3	6 (31.6%)	3 (15.8%)	9 (23.7%)
Grade 4	1 (5.3%)	1 (5.3%)	2 (5.3%)

A total of 9 patients (23.7%) experienced a Grade 3 AE and 2 patients (5.3%) experienced a Grade 4 AE. There were no Grade 5 (fatal) AEs reported. The most common Grade 3 AEs by SOC ($\geq 5\%$ of all sJIA patients) were Infections and infestations (3 patients; 7.9%), Investigations (3 patients; 7.9%), and Blood and lymphatic system disorders (2 patients; 5.3%). The only Grade 3 AE PT reported in >1 patient was Neutrophil count decreased (2 patients).

The PTs of the Grade 4 AEs were Epstein-Barr virus infection and Procedural complication. The AE Epstein-Barr virus infection was non-serious and considered related to study treatment by the investigator. There was no impact on study drug administration, as the patient was in the process of transitioning to commercial TCZ when the AE occurred. The AE resolved without sequelae. The AE Procedural complication, which occurred during a wisdom tooth extraction, was serious and not

considered related to study treatment. There was no interruption of TCZ treatment and the patient remained in the study. The AE resolved without sequelae

SAEs and death

There were no deaths reported, and no AEs with fatal outcome.

pJIA

Overall, 6 patients (13.6%) experienced 7 SAEs during the study, resulting in an SAE rate of 4.0 events per 100 PY (95% CI: 1.6, 8.3). Of the 6 patients, 5 patients experienced at least one SAE in the SOC infections and infestations. All 7 SAEs reported were NCI CTCAE Grade 1-3. The Grade 3 SAEs reported were furuncle, infectious mononucleosis, pneumonia, eye pain and headache. Three SAEs resulted in interruption of treatment (furuncle, varicella and infectious mononucleosis), but none resulted in withdrawal of treatment. No SAE PT was reported in more than 1 patient. One patient reported more than 1 SAE (this patient was hospitalized with Eye Pain and Headache; a definitive diagnosis could not be made). One SAE (PT pneumonia) was considered related to study treatment by the Investigator. The patient recovered without sequelae

sJIA

Overall, 5 patients (13.2%) experienced 6 SAEs during the study (Table 7), resulting in an SAE rate of 4.8 events per 100 PY (95% CI: 1.8, 10.4). Of the 5 patients, 3 patients experienced 3 SAEs classified as Injury, poisoning and procedural complications (craniocerebral injury [Grade 1, unrelated], procedural complication [Grade 4, unrelated], and spinal fracture [Grade 3, unrelated]), one patient experienced one SAE classified as Infections and infestations (Pneumonia mycoplasmal [Grade 3, unrelated, drug interrupted]), and one patient experienced two SAEs classified as Investigations (alanine aminotransferase increased [Grade 3, related] and aspartate aminotransferase increased [Grade 2, related]). One SAE resulted in interruption of treatment (pneumonia mycoplasmal), but none resulted in withdrawal of treatment. No SAE PT was reported in more than 1 patient. One patient reported more than 1 SAE (alanine aminotransferase increased and aspartate aminotransferase increased were reported with the same onset date in a patient receiving concomitant methotrexate). The patient recovered without sequelae

Adverse events that led to withdrawal from study treatment or from the study

pJIA

Two patients (4.5%), one in each BW group, had reported 2 AEs (neutropenia and juvenile idiopathic arthritis) that led to withdrawal from study treatment. Neither of the events was serious, however the neutropenia event was reported as NCI CTCAE Grade 4 and considered related to study treatment by the investigator, whereas the AE juvenile idiopathic arthritis (Grade 2) was considered not related to study drug.

sJIA

There were no AEs that led to withdrawal of study treatment or study

Adverse events that led to dose modification or interruption

pJIA

Overall, 20 patients (45.5%) had a total of 52 AEs that led to dose modification or interruption during the study. Infections or infestations (< 30 kg BW group: 41.7% [10 patients] and ≥ 30 kg BW group: 15.0% [3 patients]) and blood and lymphatic system disorders (< 30 kg BW group: 16.7% [4 patients] and ≥ 30 kg BW group: 5.0% [1 patient]) were the most common AEs (reported in ≥ 10% of patients

in either BW group) by SOC that led to dose modification or interruption. The most common AEs by PTs (reported in ≥ 2 patients in either BW group) that led to dose modification or interruption were neutropenia (< 30 kg BW group: 16.7% [4 patients] and ≥ 30 kg BW group: 5.0% [1 patient]), gastroenteritis (< 30 kg BW group: 12.5% [3 patients]), varicella (< 30 kg BW group: 8.3% [2 patients] and ≥ 30 kg BW group: 5.0% [1 patient]), and respiratory tract infection (< 30 kg BW group: 8.3% [2 patients]).

sJIA

Overall, 12 patients (31.6%) had a total of 32 AEs that led to dose modification or interruption during the study. The most common AEs by SOC (reported in $\geq 10.0\%$ patients in either BW group) that led to dosed modification or interruption were Infections or infestations (< 30 kg BW group: 15.8% [3 patients] and > 30 kg BW group: 31.6% [6 patients]) and Skin and subcutaneous tissue disorders (< 30 kg BW group: 0 patients and ≥ 30 kg BW group: 10.5% [2 patients]). The most common AE by PT (reported in ≥ 2 patients in either BW group) that led to dose modification or interruption was influenza (< 30 kg BW group: 10.5% [2 patients] and ≥ 30 kg BW group: 5.3% [1 patient]).

Adverse events of special interest (AESIs)

The only AESIs observed during the study were serious infection AEs and potential hypersensitivity reactions; however, none of the hypersensitivity reactions were serious or clinically significant and there were no reports of anaphylactic reactions. There were no cases of Macrophage Activation Syndrome (MAS).

All infections

pJIA

The majority of pJIA patients (42 patients, 95.5%) reported 180 AEs under the SOC of Infections and Infestations. All (100.0%) of patients in the < 30 kg BW group and 90.0% patients in the ≥ 30 kg BW group reported infection AEs over the course of this LTE study.

The majority of infections were non-serious events, all of which were reported as Grade 1-2 events. Five infection events were reported as SAEs.

There was no indication that Infection AE rates were increasing with prolonged TCZ treatment, across both BW groups, the rate was 164.7 AEs per 100-PY in Months 0-12 (95% CI: 128.6, 207.7), 133.7 AEs per 100-PY in Months 13-24 (95% CI: 100.2, 174.9), 77.0 AEs per 100-PY in Months 25-36 (95% CI: 51.2, 111.3), and 51.9 AEs per 100-PY after Month 36 (95% CI: 34.5, 75.1).

sJIA

The majority of sJIA patients (86.8%) reported at least one AE under the SOC of Infections and Infestations. A total of 94.7% of patients in the < 30 kg BW group and 78.9% patients in the > 30 kg BW group reported infection AEs over the course of this LTE study.

With the exception of one event, all the infection events were reported as non-serious infections.

There was no indication that Infection AE rates were increasing with prolonged TCZ treatment, across both BW groups the rate was 169.1 AEs per 100-PY in Months 0-12 (95% CI: 129.3, 217.2), 173.7 AEs per 100-PY in Months 13-24 (95% CI: 131.9, 224.6), 157.5 AEs per 100-PY in Months 25-36 (95% CI: 113.0, 213.6), and 113.1 AEs per 100-PY after Month 36 (95% CI: 78.3, 158.1).

Serious infections

pJIA

Overall, 5 SAEs in the SOC of Infections and infestations were experienced by 5 patients.

The PTs were appendicitis, furuncle, infectious mononucleosis, pneumonia, and varicella. Every infection SAE PT only occurred once (2.3% of all patients). Four of the five serious infections were reported to be unrelated to study treatment by the Investigator; whereas the SAE pneumonia was considered related to study treatment by the Investigator. Three of the five serious infections resulted in the TCZ treatment interruption (furuncle, infectious mononucleosis, varicella); none resulted in withdrawal of study treatment. All events were reported to have resolved, with the AE furuncle reported to have resolved with sequelae.

sJIA

Overall, 1 SAE (pneumonia mycoplasmal) in the SOC of infections and infestations was reported in 1 patient < 30 kg. The event was considered unrelated to study treatment by the Investigator, resulted in interruption of TCZ treatment, and resolved without sequelae

Hypersensitivity AEs and anaphylaxis

pJIA

Across both BW groups combined, a total of 3 patients experienced 3 potential hypersensitivity reactions (neutropenia, pyrexia, and gastroenteritis). None of the potential hypersensitivity reactions were serious (all events were either Grade 1 or 2) or clinically significant (none lead to any changes to the study treatment or study withdrawal), and all resolved without sequelae.

No anaphylaxis events occurred during the study.

sJIA

Across both BW groups combined, a total of 2 patients experienced 3 potential hypersensitivity reactions (malaise, headache, and infected cyst). None of the potential hypersensitivity events were serious (all events were either Grade 1 or 2) or clinically significant (none lead to any changes to the study treatment or study withdrawal), and all resolved without sequelae.

Selected AEs

Neutropenia Adverse Events

pJIA

Overall, 9 patients across both BW groups (8 patients in the < 30 kg BW group and 1 patient in the ≥ 30 kg BW group) experienced 27 neutropenia AEs (24 with the PT neutropenia and 3 with the PT neutrophil count decreased).

All neutropenia AEs were deemed related to study treatment by the Investigator, but none were considered serious. Fifteen neutropenia AEs experienced by 6 patients were of Grade 3 intensity, and one neutropenia AE experienced by one patient was of Grade 4 intensity. Five of the nine patients had dose interruptions as a result of neutropenia AEs (Grades 1-3) and one of these patients eventually withdrew from study treatment and eventually discontinued from the study due to a Grade 4 neutropenia AE.

There were no events of serious infections within 15 days, preceding or following, a reported neutropenia event.

sJIA

Overall, 8 patients across both BW groups combined (4 patients in the < 30 kg BW group and 4 patients in the > 30 kg BW group) experienced 14 neutropenia AEs (9 with the PT neutropenia and 5 with the PT neutrophil count decreased).

Most neutropenia AEs (78.6%) were deemed related to study treatment by the Investigator, but none were considered serious. Six neutropenia AEs experienced by 3 patients were of Grade 3 intensity. Three of the 8 patients had dose interruptions because of their neutropenia AEs (Grades 1-3)

There were no events of serious infections within 15 days, preceding or following, a neutropenia event.

Thrombocytopenia adverse events

pJIA

No thrombocytopenia AEs were reported in patients with pJIA.

sJIA

There were no events of thrombocytopenia reported in the < 30 kg BW group. Two patients weighing \geq 30 kg had one AE of thrombocytopenia each (both Grade 1). Both events were non-serious, did not lead to dose interruption, and resolved. One event was considered related to study drug by the Investigator, and the other was not.

Injection-site reactions

pJIA

Overall, ISRs occurred in 20.5% (9/44) of patients across both BW groups. The most commonly reported ISRs (occurring in \geq 2 patients) across both BW groups were injection site erythema, swelling, induration and pruritus. All ISRs reported were non-serious Grade 1 or Grade 2 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

sJIA

Overall, ISRs occurred in 7.9% (3/38) of patients across both BW groups. All reported ISRs occurred in patients \geq 30 kg. The most commonly reported ISRs (occurring in \geq 2 patients) across both BW groups were injection site erythema and swelling. All ISRs reported were non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

Clinical laboratory evaluations

Haematology

Neutrophil counts

pJIA

At baseline, 38 (86.4%) of 44 pJIA patients had a normal neutrophil count, 2 patients (4.5%) had Grade 1 low neutrophil count, 3 patients (6.8%) had Grade 2 low neutrophil count, and 1 patient (2.3%) had a missing baseline value.

Post-baseline, 16 of 44 patients (36.4%) reported neutrophil counts within the normal range throughout the study, all had a normal neutrophil count at baseline. Grade 1, 2, and 3 low neutrophil counts post-baseline were reported in 3 (6.8%), 16 (36.4%), and 6 patients (13.6%), respectively. There were 3 patients (6.8%) with Grade 4 low neutrophil counts during the study; two of these patients had a Grade 2 low neutrophil count at baseline.

There were 5 serious infections in 5 pJIA patients in this study, none of these occurred within 30 days of a low neutrophil count

sJIA

At baseline, 27 (71.1%) of 38 sJIA patients had a normal neutrophil count, 2 patients (5.3%) had Grade 1, 4 patients (10.5%) had Grade 2, 3 patients (7.9%) had Grade 3 low neutrophil count, and 2 patients (5.3%) had a missing baseline value.

Post-baseline, 14 of 38 patients (36.8%) reported neutrophil counts within the normal range throughout the study, including 13 patients who had a normal neutrophil count at baseline. Grade 1, 2, and 3 low neutrophil counts were reported in 7 (18.4%), 8 (21.1%), and 8 patients (21.1%), respectively. There was 1 patient (2.6%) with Grade 4 low neutrophil counts.

There was 1 serious infection in 1 sJIA patient in this study, which did not occur within 30 days of a low neutrophil count.

Platelet counts

pJIA

At baseline, 43 (97.7%) of the 44 pJIA patients had platelet counts within the normal range, and 1 patient (2.3%) had a missing platelet count at baseline.

Post-baseline, 38 of 44 patients (86.4%) reported platelet counts within the normal range throughout the study, including 37 patients who reported platelet counts within normal range at baseline. The 1 patient with missing platelet count at baseline reported platelet counts within the normal range throughout the study. Four patients (9.1%) had at least one Grade 1 low platelet count post-baseline, no patients had a Grade 2 or 3 low platelet count, and 2 patients (4.5%) had at least one Grade 4 low platelet count.

Eight patients experienced 9 bleeding events in this study, none of these occurred within 30 days of a low platelet count.

sJIA

At baseline, 34 (89.5%) of 38 sJIA patients had platelet counts within the normal range, 3 patients (7.9%) had a Grade 1 low platelet count and 1 patient (2.6%) had a missing platelet count at baseline.

Post-baseline, 24 of 38 (63.2%) patients reported platelet counts within the normal range throughout the study, including 22 patients who had normal baseline platelet count. Over the course of the study, 13 patients (34.2%) had at least one Grade 1 low platelet count post-baseline, no patients had a Grade 2 or 3 low platelet count, and 1 patient (2.6%) had at least one Grade 4 low platelet count. Of the 3 patients who had a Grade 1 low platelet count at baseline, 1 patient (2.6%) had platelet counts within the normal range post-baseline, and 2 patients (5.3%) did not have lower platelet counts than Grade 1 post-baseline. The 1 patient with missing platelet count at baseline reported platelet counts within the normal range throughout the study.

The patient (< 30kg: 1 patient [5.3%]) who had a platelet count depression to Grade 4 post-baseline had only one such platelet count depression at a single time point. A repeat test done locally by the study site did not confirm this result but showed normal platelet count.

Eight patients experienced 15 non-serious bleeding events in this study, none of these occurred within 30 days of a low platelet count.

Chemistry

Liver enzymes (ALT and AST) and bilirubin

There were no patients who met the laboratory criteria for Hy's law, that is, no patients in this study were identified as having a ≥ 3 x the ULN elevation in AST or ALT accompanied by a ≥ 2 x ULN in total bilirubin. There were also no serious hepatic AEs in this study.

Lipid parameters

pJIA

Of the 38 patients with lipids assessed (including patients with elevated lipids at baseline), 11 patients experienced a post-baseline elevation of their total cholesterol value to ≥ 200 mg/dL at any time during study treatment. Three patients (7.9%) had an elevation at a single time point, 3 (7.9%) had consecutive elevations, 3 (7.9%) had consecutive sustained elevations, and 2 patients had non-consecutive elevations (5.3%). Six patients experienced a post-baseline elevation of their LDL cholesterol value to ≥ 130 mg/dL at any time during study treatment. Two patients (5.3%) had an elevation at a single time point, 1 (2.6%) had consecutive elevations, 2 (5.3%) had consecutive sustained elevations, and 1 patient had non-consecutive elevations (2.6%).

sJIA

Of the 32 patients with lipids assessed (including patients with elevated lipids at baseline), 9 patients experienced a post-baseline elevation of their total cholesterol value to ≥ 200 mg/dL at any time during study treatment. Three patients (9.4%) had an elevation at a single time point, 1 (3.1%) had consecutive sustained elevations, and 5 patients had non-consecutive elevations (15.6%). Five patients experienced a post-baseline elevation of their LDL cholesterol value to ≥ 130 mg/dL at any time during study treatment. One patient (3.1%) had consecutive elevations, and 4 patients had non-consecutive elevations (12.5%).

Vital Signs

pJIA

The majority of patients (range: 75.0% - 97.7%) did not experience abnormally high or low SBP, DBP, or heart rate during the study.

sJIA

The majority of patients (range: 68.4% - 86.8%) did not experience abnormally high or low SBP, DBP, or heart rate during the study.

Chest X-rays and tuberculosis (TB) tests

pJIA

One patient (in the < 30 kg BW group) had an abnormal chest X-ray on Study Day 1560; the result was reported as not clinically significant by the investigator.

No patient reported a positive Quantiferon TB test result or Purified Protein Derivative (PPD) test result ≥ 5 mm at screening.

Two patients (both in the < 30 kg BW group) had a PPD skin test result ≥ 5 mm during the study, one at Study Day 1092 and one at Study Day 1597. For one of these patients the investigator judged the test result (10 mm) as being positive and the patient was reported to have latent TB; TCZ treatment was interrupted and the patient was treated with a full course of Isoniazid. TCZ treatment was resumed a few weeks after the patient had initiated Isoniazid. For the other patient, the PPD skin test

result (5 mm) was judged as being negative by the investigator. No patient had a positive Quantiferon TB test in the study.

sJIA

One patient (in the < 30 kg BW group) had an abnormal chest X-ray on Study Day 1475; the result was reported as not clinically significant by the investigator.

No patient reported a positive Quantiferon TB test result or PPD test result \geq 5 mm at screening. One patient (in the \geq 30 kg BW group) had a PPD skin test result \geq 5 mm at Study Day 403. The test result (7 mm) was judged as being negative by the investigator. No patient had a positive Quantiferon TB test in the study

Pregnancies

One pJIA patient in the \geq 30kg BW group had a positive pregnancy test on study day 637. Due to the pregnancy, the patient immediately withdrew from TCZ treatment and subsequently discontinued from the study after an induced abortion failed. The pregnancy continued following the patient's discontinuation from the study and the patient gave birth to a live born baby at full term (38 weeks).

There were no pregnancies reported in sJIA patients.

Pharmacokinetics

Pharmacodynamics

Soluble IL-6 receptor (sIL-6R)

In pJIA and sJIA patients, sIL-6R levels did not fluctuate significantly over the time course of the study.

Interleukin-6 (IL-6)

pJIA

In pJIA patients, median (range) IL-6 levels were steady over time,

sJIA

In patients with sJIA, IL-6 levels slightly decreased from baseline to Week 144, with median (range) values of 26.70 (5.29-297.00) pg/mL and 17.60 (10.00-11160.00) pg/mL, respectively.

Immunogenicity

pJIA

A total of 41/44 patients were classified as post-baseline evaluable. Of the 3 patients who were not post-baseline evaluable, one patient did not have a baseline sample collected. Two patients (one in the < 30 kg BW group and one in the \geq 30 kg BW group) had a positive confirmatory assay at the LTE study baseline visit, but neither patient had any positive results post-baseline. Both of these patients had already been positive for treatment-induced ADA in their last core study assessment.

Of the 41 post-baseline evaluable patients, there were no treatment-induced ADA reported in the < 30 kg BW group. However, there were two patients in the \geq 30 kg BW group who presented with treatment-induced ADAs; both patients developed ADA of neutralizing potential and neither developed ADAs of the IgE isotype.

One patient had two post baseline ADA samples with a positive confirmatory assay and confirmed neutralizing potential, at Week 48 and Week 72, but had no impact on the PK profile. The patient did not experience any hypersensitivity reactions (excluding ISRs) or ISRs and completed the study.

The other patient had one positive confirmatory assay result at Week 48 (Day 337), with confirmed neutralizing potential. In this patient, TCZ concentration at baseline was slightly higher than the median C_{trough} reported in the Q2W dosing group (12.5 $\mu\text{g/mL}$ vs 8.09 $\mu\text{g/mL}$). Exposure values at Week 24 and Week 48 (1.13 $\mu\text{g/mL}$ and 3.33 $\mu\text{g/mL}$, respectively) were below the observed median concentration (8.79 $\mu\text{g/mL}$ and 7.87 $\mu\text{g/mL}$, respectively). It should be noted though that the TCZ concentration at Week 24 of the patient was excluded from the analysis due to compliance issues. A direct impact of ADAs on TCZ exposure is therefore difficult to assess, but cannot be fully excluded.

This patient did not experience any hypersensitivity reactions but did experience several ISRs (injection site erythema, injection site haematoma, injection site swelling, and injection site pruritus), all ISRs were non-serious CTCAE Grade 1 events considered related to TCZ treatment by the investigator, did not lead to study treatment interruption, and resolved without sequelae. The patient was discontinued on Day 452 (Week 64) for lack of efficacy.

sJIA

A total of 37/38 sJIA patients were classified as post-baseline evaluable. Of these 37 patients, none developed ADA against TCZ during the study period.

2.3.4. Discussion on clinical aspects

Study WA29231 was the LTE study of the JIGSAW studies (Study WA28117 in patients with pJIA and Study WA28118 in patients with sJIA) to support the use of TCZ SC in paediatric population. Patients diagnosed with pJIA or sJIA according to ILAR classification (Petty et al. 2004) who have completed treatment and had an adequate response to TCZ SC in the JIGSAW studies were eligible for the LTE study. Patients were stratified according to the bodyweight i.e. < 30 kg and > 30 kg.

Patients received 162 mg SC TCZ according to body weight (BW) and JIA subtype, which is in line with the authorised posology.

The objectives of the study were to evaluate the long-term safety and efficacy of SC administration of TCZ in patients with pJIA and sJIA. The study period for efficacy was 3 years and for safety 5 years (planned)

Of the 44 pJIA patients enrolled in the LTE Study a total of 19 patients (43.2%) completed the study and of the 38 sJIA patients enrolled in the LTE study 6 patients completed the study. In the pJIA group 2 patients discontinued due to an AE safety reason, all other patients discontinued to non-safety reasons. Altogether 24 patients were transferred to commercially available TCZ.

Over the 3-year study period where efficacy was assessed, JIA remained controlled in both pJIA and sJIA patients, irrespective of BW group. Patients remained stable over time for the efficacy variables assessed across pJIA and sJIA patients and in both BW groups.

The safety results observed were consistent with the established safety profile of TCZ in pJIA and sJIA in both BW groups. No new safety signals were identified with long-term treatment over 5 years.

3. CHMP overall conclusion and recommendation

Over the 3-year study period where efficacy was assessed, JIA remained controlled in both pJIA and sJIA patients, irrespective of BW group. Patients remained stable over time for the outcomes variables assessed across pJIA and sJIA patients and in both BW groups.

The safety results observed were consistent with the established safety profile of TCZ in pJIA and sJIA in both BW groups. No new safety signals were identified with long-term treatment over 5 years.

Fulfilled:

No regulatory action required.