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Human Medicines Division

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

RoActemra

Tocilizumab

Procedure no: EMA/PAM/0000348681

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

1. Introduction

On 12 May 2026, the MAH submitted a completed paediatric study for RoActemra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study WA29358: Observational safety and effectiveness study of patients with polyarticular juvenile idiopathic arthritis treated with tocilizumab is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Use of commercial product

2.3. Clinical aspects

Introduction

The MAH submitted a final report for:

- Study WA29358: Observational safety and effectiveness study of patients with polyarticular juvenile idiopathic arthritis treated with tocilizumab

Clinical study WA29358: Observational safety and effectiveness study of patients with polyarticular juvenile idiopathic arthritis treated with tocilizumab

Description

This was an international, multicenter, prospective, observational-cohort study to examine the long-term safety and effectiveness data from patients with pJIA treated with TCZ IV 8 mg/kg (10 mg/kg in patients weighing< 30 kg) Q4W or TCZ SC 162 mg every 2 weeks (every 3 weeks in patients weighing<30 kg), or a comparator biologic), with or without a disease-modifying antirheumatic drug (DMARD).

The study allowed for analysis of aggregate data from approximately 600 patients with pJIA who were enrolled in national disease or treatment registries (i.e., feeder registries) in the United States and Germany, at approximately 100 sites. The study included a control group of paediatric pJIA patients treated with other biologics as standard of care.

The observation period was defined as a maximum of 5 years for patients initiating treatment with TCZ (IV or SC) or a comparator biologic. Patients who discontinued or switched therapy during the observation period continued to be followed in accordance with feeder registry protocols to allow for long-term safety assessment up to the maximum 5-year period.

The three feeder registries were:

- Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry (United States)
- Juvenile arthritis MTX/Biologics long-term Observation (JuMBO) registry (Germany)
- Biologics in Paediatric Rheumatology Registry (BiKeR) (Germany)

Methods

Study participants

Patients enrolled in the feeder registries met all of the following criteria for inclusion in this study:

- Diagnosis of pJIA, defined according to ILAR classification (Petty et al. 2004):
  - Patients with RF-positive pJIA
  - Patients with RF-negative pJIA
  - Patients with eoJIA
- Initiation of treatment with TCZ (IV or SC) or a comparator biologic
  - The TCZ group will include patients with no previous exposure to TCZ (IV or SC). The comparator biologic group will include patients with no previous exposure to that specific comparator biologic.
- Age ≤ 17 years at the time of initiation of treatment with TCZ (IV or SC) or a comparator biologic

Treatments

TCZ IV 8 mg/kg (10 mg/kg in patients weighing <30 kg) Q4W or TCZ SC 162 mg every 2 weeks (every 3 weeks in patients weighing <30 kg), or a comparator biologic.

Objective

The overall objective of the study was to assess the long-term safety and effectiveness of TCZ (IV or SC) in relation to a comparator biologic in the treatment of pJIA in a real-world setting for 5 years.

Outcomes/endpoints

The safety objectives for the study were the following:

- To assess in routine clinical practice the rate of serious adverse events (SAEs) and the rates of adverse events (AEs) in predefined categories of special interest (infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], GI perforations [serious], and uveitis events [serious and non-serious]) in pJIA patients treated with TCZ (IV or SC) or a comparator biologic
- To assess in routine clinical practice the rate and treatment outcome of uveitis in pJIA patients treated with TCZ (IV or SC) or a comparator biologic on the basis of available data from the feeder registries
- To assess in routine clinical practice the growth (relative to age-specific standards for height and weight) of pJIA patients treated with TCZ (IV or SC) or a comparator biologic
- To assess in routine clinical practice the development (via self-reported or examined Tanner staging) of pJIA patients treated with TCZ (IV or SC) or a comparator biologic on the basis of available data from the feeder registries

The effectiveness objectives for the study were the following:

- To assess in routine clinical practice the effectiveness of TCZ (IV or SC) in patients with RF-positive and RF-negative pJIA, as determined on the basis of Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10)
- To assess in routine clinical practice the effectiveness of 10 mg/kg TCZ in pJIA patients weighing < 30 kg at treatment initiation, as determined on the basis of JADAS-10

Sample size

Approx. 600 patients

Randomisation and blinding (masking)

N/A, no protocol-mandated treatment assignment in the feeder registries

Statistical Methods

Descriptive statistics

Data was summarized by TCZ and Non-TCZ comparator groups.

Results

Participant flow

A total of 344 patients and 345 patients were enrolled in the TCZ cohort and Non-TCZ cohort of the study, respectively.

Study discontinuation

The number of patients who completed the study in the TCZ cohort (236 patients [68.6%]) is comparable to the Non-TCZ cohort (238 patients [69.0%]) of the study. A total of 108 patients (31.4%) discontinued from the TCZ cohort as compared to the 107 patients (31.0%) who discontinued from the Non-TCZ cohort.

Lost to follow-up was the main reason for discontinuation from the study for both the TCZ cohort (93 patients [27.0%]) and Non-TCZ cohort (83 patients [24.1%]). There was a difference in the proportion of patients who switched off treatment between the TCZ cohort (75 patients [21.8%]) and Non-TCZ cohort (38 patients [11.0%]).

Tabel 1: Study disposition, all patient population

Study Disposition, All Patient Population
Protocol: WA29358

Reason for Discontinuation:	TCZ (N=344)	Non-TCZ (N=345)
Enrolled Subjects	344 (100.0%)	345 (100.0%)
Completed	236 (68.6%)	238 (69.0%)
Discontinued:	108 (31.4%)	107 (31.0%)
Adverse Event	0 (0.0%)	1 (0.3%)
Pregnancy	0 (0.0%)	0 (0.0%)
Death	1 (0.3%)	2 (0.6%)
Lost to Follow-up	93 (27.0%)	83 (24.1%)
Protocol Deviation	0 (0.0%)	0 (0.0%)
Non-Compliance	3 (0.9%)	0 (0.0%)
Withdrawal by Subject	7 (2.0%)	9 (2.6%)
Study Terminated by Sponsor	0 (0.0%)	0 (0.0%)
Physician Decision	0 (0.0%)	0 (0.0%)
Other	4 (1.2%)	12 (3.5%)
Subjects Switched/Re-Enrolled	75 (21.8%)	38 (11.0%)
Enrolled by Age:		
0 to 2	5 (1.5%)	19 (5.5%)
3 to 6	29 (8.4%)	57 (16.5%)
7 to 12	143 (41.6%)	125 (36.2%)
13 to 17	167 (48.5%)	144 (41.7%)
Enrolled by Weight:*		
<30kg	56 (16.3%)	46 (13.3%)
>=30kg	287 (83.4%)	125 (36.2%)
Number of patients who switched off treatment:		
Year 1	59 (17.2%)	47 (13.6%)
Year 2	38 (11.0%)	32 (9.3%)
Year 3	26 (7.6%)	17 (4.9%)
Year 4	30 (8.7%)	26 (7.5%)
Year 5	8 (2.3%)	7 (2.0%)

* Non-TCZ data from CARRA registry only.
Percentages are based on N.

Treatment Discontinuation

The main reason for treatment discontinuation in the TCZ cohort was ineffectiveness (lack of primary response) (24.7% in TCZ cohort vs.16.2% in Non-TCZ cohort), whereas in the Non-TCZ cohort was disease well-controlled (19.1% in Non-TCZ cohort vs 16.0% in TCZ cohort). This higher rate of discontinuation due to ineffectiveness in the TCZ group must be interpreted in the context of the baseline profiles, the TCZ cohort represented a significantly more difficult-to-treat and treatment-refractory population, as 86.3% of these patients had already failed at least one prior biologic, compared to only 23.5% in the Non-TCZ group.

The proportion of patients with an unknown reason for treatment discontinuation was substantially higher in the Non-TCZ cohort (12.2%) compared to the TCZ cohort (4.9%). Other reasons for treatment discontinuation included disease flare (6.4% in the TCZ cohort versus (vs.) 3.2% in the Non-TCZ cohort), chronic non-adherence (3.5% vs. 2.9%, respectively) and 0.6% (2 patients) pregnancies in the Non-TCZ cohort only.

Tabel 2: Treatment disposition, all patient population

Treatment Disposition, All Patient Population
Protocol: WA29358

Reason for Discontinuation:	TCZ (N=344)	Non-TCZ (N=345)
Chronic non-adherence	12 (3.5%)	10 (2.9%)
Disease flare	22 (6.4%)	11 (3.2%)
Disease well-controlled	55 (16.0%)	66 (19.1%)
Family fear of potential serious adverse event	0 (0.0%)	1 (0.3%)
Financial cost	0 (0.0%)	2 (0.6%)
Ineffective (lack of primary response)	85 (24.7%)	56 (16.2%)
Infusion/Injection reaction	2 (0.6%)	1 (0.3%)
Interval patient growth (outgrown dose)	2 (0.6%)	0 (0.0%)
Intolerance of medication or delivery method	16 (4.7%)	14 (4.1%)
Other, specify: _____	25 (7.3%)	23 (6.7%)
Planned dose change (e.g. gradually increasing dose based on tolerance)	1 (0.3%)	0 (0.0%)
Pregnancy	0 (0.0%)	2 (0.6%)
Surgery, specify: _____	0 (0.0%)	0 (0.0%)
Unknown	17 (4.9%)	42 (12.2%)
Uveitis, active	1 (0.3%)	2 (0.6%)

Percentages are based on N.

Recruitment

The data collection by the feeder registries was from 10 June 2013 to 30 June 2025.

Baseline data

Baseline demographics were comparable between the TCZ (n=344) and Non-TCZ (n=345) cohorts. Both groups were predominantly female (81.7%) and White (66.0% TCZ vs. 73.3% Non-TCZ), with mean ages of 12.4 and 11.0 years, respectively.

The TCZ cohort had a higher proportion of patients weighing ≥30 kg (265 vs. 223) and exhibited a more treatment-refractory profile, with substantial higher prior use of biologics (86.3% vs. 23.5%), MTX (75.9% vs. 54.2%), and systemic steroids (41.6% vs. 26.4%). JIA subtypes were similarly distributed, led by RF-negative polyarthritis (~63%), followed by eoJIA and RF-positive polyarthritis.

Within the TCZ sub-population weighing <30 kg (n=38; mean age 7.63), 73.7% had RF-negative polyarthritis, 92.1% had prior biologic exposure, and 73.7% had prior MTX use, further underscoring the high treatment burden in this group.

Efficacy results

Real-world effectiveness was demonstrated by a reduction in JADAS-10 scores (change from baseline ranged from -8.98 to -9.78 over Years 1 to 5). Despite the TCZ cohort representing a more treatment-refractory population, with 86.3% having failed at least one prior biologic compared to only 23.5% in the Non-TCZ group, TCZ-treated patients achieved and maintained low disease activity (see Section 4.1.2). In the RF-negative polyarthritis subgroup, the mean JADAS-10 improved from 12.83 at baseline to 2.73 at Year 3. The results from this analysis of the combined feeder registry data are in alignment with the existing controlled trial data, confirming that the effectiveness observed in controlled settings translates effectively into real-world clinical practice. No conflicting findings were identified between this study and previous major paediatric JIA clinical trial results.

Despite a more refractory baseline profile, the TCZ cohort achieved clinical disease control comparable to the Non-TCZ group, confirming its efficacy in patients who have failed prior tumour necrosis factor (TNF)-inhibitor therapy.

Tabel 3: Effectiveness: JADAS-10 Score, all patient population

Effectiveness: JADAS-10 Score, All Patient Population
Protocol: WA29358

	TCZ (N=344)	TCZ Change from Baseline (N=344)
Baseline		
n	285	
Mean (SD)	13.23 (7.07)	
Min - Max	0.0 - 30.9	
Year 1		
n	179	169
Mean (SD)	4.57 (5.58)	-8.98 (7.47)
Min - Max	0.0 - 24.0	-26.0 - 12.0
Year 2		
n	125	116
Mean (SD)	2.57 (3.94)	-9.89 (7.11)
Min - Max	0.0 - 21.4	-25.8 - 5.5
Year 3		
n	84	78
Mean (SD)	2.98 (4.71)	-9.28 (8.09)
Min - Max	0.0 - 19.3	-25.6 - 18.5
Year 4		
n	62	59
Mean (SD)	2.53 (3.33)	-9.12 (6.62)
Min - Max	0.0 - 13.0	-23.6 - 8.0
Year 5		
n	33	32
Mean (SD)	3.18 (5.62)	-9.78 (6.66)
Min - Max	0.0 - 19.4	-21.8 - 12.5

JADAS = Juvenile Arthritis Disease Activity Score.

At baseline, patients in the <30 kg subgroup exhibited high disease activity, with a mean (standard deviation [SD]) JADAS-10 score of 15.34 (6.36) (n=26). Following the initiation of TCZ therapy, disease activity decreased substantially. This clinically meaningful reduction was sustained over the 5-year observation period among the evaluable patients who remained on therapy. While the mean JADAS-10 score reached 0 at Year 5, this specific long-term result must be interpreted cautiously due to data attrition over time (n=4 evaluable patients at Year 5). Nonetheless, the consistent trajectory of the available longitudinal data confirms a durable and robust clinical response for this paediatric weight subgroup.

Data for this observational cohort study were derived from feeder registries in the United States and Germany. Given the lack of randomization and potential regional variations in standards of care, the generalizability of these findings to other geographic populations should be interpreted with caution.

Safety results

Serious Adverse Events

Serious adverse events in the CARRA and BiKeR/JuMBO registries combined were reported in the On treatment patient population output. The number of SAEs in the TCZ cohort were 25 SAEs (AE rate per 100 PY= 2.6%) (95% CI for AE rate per 100 years= 1.7, 3.9) for 18 patients (5.23%), was higher than reported in the Non-TCZ cohort which were 19 SAEs (AE rate per 100 PY= 1.6%) (95% CI for AE rate per 100 years=0.9, 2.4) for 13 patients (3.77%).

SAE from the BiKeR/ JuMBO registries in On-Treatment population and Ever-treated population are presented below:

- On-Treatment population: SAEs reported in 14 patients (8.2%) in TCZ cohort, with the most commonly reported serious adverse event as suicidal ideation (2 patients [1.2%]). In the Non-TCZ cohort, reported SAEs in 11 patients (6.4%) with the most commonly reported SAEs, juvenile idiopathic arthritis and depression (2 patients [1.2%] each) in the Non-TCZ cohort.

- In the Ever-treated population: SAEs were reported for 31 patients (18.1%) in TCZ cohort and for 16 patients (9.4%) in the Non-TCZ cohort.
    - For the TCZ cohort, the most commonly reported SAE were drug ineffective, juvenile idiopathic arthritis and suicidal ideation (3 patients [1.8%] each), abdominal pain, fracture and arthritis (2 patients [1.2%] each).
    - For the Non-TCZ cohort, the most commonly reported SAE were drug ineffective, juvenile idiopathic arthritis, depression and post-traumatic stress disorder (2 patients [1.2%] each).
- All other SAEs for On-Treatment and Ever-Treated populations were reported as single incidence.

Adverse Events of Special Interest

The type of serious infections were identical in both cohorts, and the incidence of serious infections was uncommon in both cohorts (0.3 events per 100 patient-years), confirming no cumulative or disproportionate infectious risk with long-term exposure. Serious infections are part of the known safety profile of TCZ.

The risk of atherosclerosis was assessed by monitoring cardiovascular events. During the 5-year observation period, no atherosclerotic or ischemic cardiovascular events (e.g., myocardial infarction) were reported in either cohort. Within the TCZ cohort, only a single, non-atherosclerotic cardiovascular event (cardiac failure) was reported, thereby indicating no increased risk of atherosclerosis in the pJIA population.

Notably, the exposure-adjusted incidence rate of uveitis was lower in the TCZ cohort (0.6 events per 100 patient-years) compared to the Non-TCZ cohort (2.2 events per 100 patient-years (Table below). This finding is particularly relevant given that a substantially higher proportion of patients in the TCZ cohort had a pre-existing medical history of uveitis at baseline (10.5% in the TCZ cohort vs. 3.5% in the Non-TCZ cohort). All uveitis events reported in the TCZ group were non-serious. In two of the uveitis cases, treatment with TCZ was discontinued, and in four cases the dosing remained unchanged. Participants in the TCZ cohort with uveitis reported the use of other DMARDs concomitantly with TCZ.

The study did not report malignancies or GI perforations in either cohort. The incidence rates of other AESIs in both the cohorts were comparable. No new safety signal specific to the paediatric population was identified for TCZ.

Tabel 4: Adverse Events of Special Interest Rate per 100 years of Patients Affected and 95% CI

	TCZ Cohort			Non-TCZ Cohort		
	Non-serious Uveitis	Serious infections	Cardiovascular Events	Non-serious Uveitis	Serious infections	Cardiovascular Events
No. of AEs reported	6	3	1	27	4	0
AE rate per 100 years	0.6	0.3	0.1	2.2	0.3	NA
95% CI for AE rate per 100 years	0.2, 1.4	0.1, 0.9	0.0, 0.4	1.5, 3.2	0.1, 0.8	NA
No. of patients with events	5	3	1	20	4	0
Rate of Patients affected	1.45%	0.87%	0.29%	5.8%	1.16%	NA

AE = adverse event; AESI = Adverse Events of Special Interest; CI = confidence interval; NA = not applicable; TCZ = tocilizumab.

Death

A total of 2 deaths were reported during the study period. Neither death was reported to be related to study medication. One fatal event occurred in a patient exclusively in the Non-TCZ cohort (approximately 22 months after the 90-day risk window extension). The second fatal event occurred in a patient exposed to both cohorts (approximately 8 months after the TCZ risk window and 17 months after the Non-TCZ risk window).

Adverse Events leading to Treatment Discontinuation

Treatment discontinuation rates due to AEs were comparable between the TCZ (3.8%) and Non-TCZ (4.1%) cohorts, with similar exposure-adjusted rates of 1.44 and 1.19 per 100 patient-years, respectively.

Development and Growth Patterns

At baseline, both cohorts had slightly negative mean height Standard Deviation Score (SDS) (TCZ: -0.25; Non-TCZ: -0.32), indicating that the patients were, on average, slightly shorter than their healthy age- and sex-matched peers which is typical of chronic paediatric inflammation (d'Angelo et al. 2021). However, the longitudinal outputs show no decrease in mean height SDS over 5 years. Instead, scores improved continuously, normalizing by Year 5 (TCZ: 0.02; Non-TCZ: -0.15).

There was no impact of treatment on the overall height, growth and development of the participants in either of the two cohorts. While participants in the TCZ cohort were older and represented fewer developmental patterns (except post-pubertal categories), both cohorts showed comparable height SDS and experienced improvement in growth over five years. The findings support the effectiveness of both TCZ and Non-TCZ treatment regimens in preserving growth velocity, regardless of age or developmental maturity at treatment onset.

Longitudinal data on growth (SDS) and Tanner staging indicated that TCZ treatment does not impact normal physical and pubertal development in paediatric patients.

Discussion on clinical aspects

Study WA29358 was a 5-year, observational real-world study evaluating the long-term safety and effectiveness of tocilizumab (TCZ) compared with a comparator biologic in paediatric pJIA patients,

based on data from three feeder registries in the United States and Germany. As treatment allocation was not protocol-mandated, but based on physician choice, baseline differences between cohorts were observed. Patients receiving TCZ were slightly older and were more likely to weigh above 30 kg and had a more treatment-refractory disease profile, including greater prior exposure to biologics, MTX, and systemic corticosteroids, while other baseline characteristics were generally comparable. These baseline differences, together with the possibility of treatment switching, should be considered when interpreting the results of this study, as they may limit direct comparisons between the treatment groups.

The study demonstrated sustained effectiveness of TCZ in the paediatric population, with minimal disease activity achieved and maintained during the study, as reflected by reductions in the JADAS-10 score from baseline. Efficacy was also observed in patients weighing <30 kg; however, long-term effectiveness data in this subgroup remain very limited.

Although the overall number of SAEs was higher in the TCZ cohort, the incidence rates of serious infections and serious cardiovascular events were comparable between treatment groups. Fewer uveitis events were reported in the TCZ cohort than in the non-TCZ cohort, and only 2 of the 6 patients with uveitis discontinued TCZ treatment. One non-atherosclerotic cardiovascular event (cardiac failure) was reported in the TCZ cohort. The MAH's conclusion that the single non-atherosclerotic event indicates no increased risk of atherosclerosis in the paediatric population is not sufficiently supported by the provided data. In paediatric patients, atherosclerosis is typically subclinical and unlikely to result in symptomatic cardiovascular events during childhood. Therefore, the absence of reported atherosclerotic cardiovascular events cannot be interpreted as evidence for the absence of an increased risk of atherosclerosis.

No cases of malignancy, gastrointestinal perforation, or serious uveitis were reported, and no adverse effects on growth or development were identified. Overall, the study did not reveal any new safety concerns.

3. Rapporteur's overall conclusion and recommendation

The findings from Study WA29358 support a favourable long-term benefit-risk profile for tocilizumab (TCZ) in paediatric pJIA patients. The collected safety data are consistent with the known safety profile. No amendment of the product information is warranted.

The benefit/risk ratio for RoActemra remains unchanged.

☒ **Fulfilled:**

No regulatory action required.