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Original article

Subcutaneous dosing regimens of tocilizumab in children with systemic or polyarticular juvenile idiopathic arthritis

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Abstract

Objectives. To determine s.c. tocilizumab (s.c.-TCZ) dosing regimens for systemic JIA (sJIA) and polyarticular JIA (pJIA).

Methods. In two 52-week phase 1 b trials, s.c.-TCZ (162 mg/dose) was administered to sJIA patients every week or every 2 weeks (every 10 days before interim analysis) and to pJIA patients every 2 weeks or every 3 weeks with body weight $\geq$30 kg or $<$30 kg, respectively. Primary end points were pharmacokinetics, pharmacodynamics and safety; efficacy was exploratory. Comparisons were made to data from phase 3 trials with i.v. tocilizumab (i.v.-TCZ) in sJIA and pJIA.

Results. Study participants were 51 sJIA patients and 52 pJIA patients aged 1–17 years who received s.c.-TCZ. Steady-state minimum TCZ concentration (C_{trough}) $>$5th percentile of that achieved with i.v.-TCZ was achieved by 49 (96%) sJIA and 52 (100%) pJIA patients. In both populations, pharmacodynamic markers of disease were similar between body weight groups. Improvements in Juvenile Arthritis DAS-71 were comparable between s.c.-TCZ and i.v.-TCZ. By week 52, 53% of sJIA patients and 31% of pJIA patients achieved clinical remission on treatment. Safety was consistent with that of i.v.-TCZ except for injection site reactions, reported by 41.2% and 28.8% of

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sJIA and pJIA patients, respectively. Infections were reported in 78.4% and 69.2% of patients, respectively. Two sJIA patients died; both deaths were considered to be related to TCZ.

Conclusion. s.c.-TCZ provides exposure and risk/benefit profiles similar to those of i.v.-TCZ. S.c. administration provides an alternative administration route that is more convenient for patients and caregivers and that has potential for in-home use.

Trial registration. ClinicalTrials.gov, http://clinicaltrials.gov, NCT01904292 and NCT01904279

Key words: autoinflammatory conditions, biologic therapies, cytokines and inflammatory mediators, inflammation, juvenile idiopathic arthritis

Rheumatology Key messages

- Subcutaneous tocilizumab dosing in JIA was determined by bridging to data for intravenous tocilizumab.
- Subcutaneously administered tocilizumab has a risk/benefit profile similar to that of intravenous tocilizumab dosing regimens.
- Subcutaneous tocilizumab provides an alternative administration route that is more convenient for patients and caregivers.

Introduction

JIA is classified into mutually exclusive categories [1–3]. Children with polyarticular JIA (pJIA) have a more refractory disease course than those who have fewer affected joints, and they are at risk for severe disability [4, 5]. Systemic JIA (sJIA) is characterized by autoinflammatory and autoimmune disease features [6, 7].

IL-6 plays a central role in the pathogenesis of JIA, and levels correlate positively with the severity of joint involvement, systemic disease features, and markers of inflammation such as CRP [8–11]. Tocilizumab (TCZ) is a humanized monoclonal anti–IL-6 receptor (IL-6R)-alpha antibody that inhibits IL-6 function [12, 13]. Phase 3 randomized controlled trials demonstrated that i.v.-TCZ was an effective treatment for sJIA [14], pJIA [15] and RA [16, 17]. In RA, s.c.-TCZ has efficacy and safety comparable with those of i.v.-TCZ [18, 19]. S.c. injections offer a convenient alternative to i.v. administration by allowing administration by the patient or caregiver, eliminating the inconvenience of short hospital admission for infusions and reducing the stress of i.v. administration, which is particularly relevant for younger children [20, 21].

We report results of two clinical trials in children with sJIA and pJIA conducted to identify optimal dosing regimens of s.c.-TCZ.

Patients and methods

Study designs

The sJIA trial (ClinicalTrials.gov, NCT01904292) and the pJIA trial (ClinicalTrials.gov, NCT01904279) were 52-week, open-label, multicentre, pharmacokinetic (PK), pharmacodynamic (PDy) and safety phase 1 b studies designed to identify s.c.-TCZ dosing regimens that would achieve TCZ exposure [steady-state minimum TCZ concentration (C_{trough})] comparable with that of i.v.-TCZ dosing regimens [14, 15]. Based on PK analyses from i.v.-TCZ trials in sJIA and pJIA (Supplementary Data S1, available at *Rheumatology* online), a dose of 162 mg s.c.-TCZ once weekly [QW; 162 mg every 10 days (Q10D) for patients weighing $<$30 kg] for sJIA and 162 mg s.c.-TCZ every 2 weeks [Q2W; 162 mg every 3 weeks (Q3W) for patients weighing $<$30 kg] for pJIA was expected to provide exposures comparable with those of i.v.-TCZ. CONSORT [22] reporting was followed as applicable. A sample size of 48 patients in each study was considered adequate to provide $\geq$80% power to have the 95% CI fall within 60% and 140% of the population mean estimates for the PK parameters in paediatric age groups [23].

Patients

Children aged 1–17 years (12–17 years in Russia) with sJIA or pJIA (RF-positive or RF-negative polyarticular and extended oligoarticular JIA) according to the ILAR criteria were eligible [24]. sJIA patients were enrolled from 15 August 2013 through 28 June 2016 at 26 centres, and pJIA patients were enrolled from 24 July 2013 through 27 May 2015 at 24 centres in 11 countries in the Paediatric Rheumatology INternational Trials Organisation (PRINTO) and the Paediatric Rheumatology Collaborative Study Group (PRCSG) networks [25, 26].

Patients in the sJIA trial had inadequate responses to NSAIDs and glucocorticoids. Patients in the pJIA trial had inadequate responses or intolerance to MTX. Eligible patients were TCZ-naive or had achieved well-controlled sJIA or pJIA with i.v.-TCZ (TCZ-prior). Patients for whom i.v.-TCZ was discontinued for lack of efficacy or safety reasons were excluded. Full eligibility criteria are in Supplementary Data S2, available at *Rheumatology* online. To adequately characterize the

absorption of s.c.-TCZ, ≥50% of the total population was TCZ-naive at baseline. TCZ-prior patients received their first dose of s.c.-TCZ at their next scheduled date of i.v.-TCZ. Concomitant treatment with oral glucocorticoids (doses at the investigator's discretion), NSAIDs and non-biologic DMARDs, including MTX, was allowed. Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and informed consent was obtained from all patients and/or parents. The protocols were approved by institutional review boards or independent ethics committees at each site.

Assessments

Primary PK and PDy objectives were to evaluate s.c.-TCZ in patients with sJIA or pJIA to identify fixed-dosing regimens of TCZ 162 mg that provide TCZ exposures similar to those achieved with i.v.-TCZ. Blood samples for PK/PDy analysis were obtained per protocol (Supplementary Data S3, available at *Rheumatology* online). Safety assessments included adverse events (AEs), serious AEs (SAEs) and laboratory parameters. AEs were classified using the Medical Dictionary for Regulatory Activities 20.0 (sJIA) or 19.0 (pJIA). Efficacy was an exploratory objective. Anti-TCZ antibodies were assayed at prespecified intervals with a tiered testing strategy [27].

Exploratory efficacy measures included disease activity measured by Juvenile Arthritis DAS including 71 joints (JADAS-71) (cut-off scores for pJIA: high disease activity, >10.5; moderate disease activity, 3.9–10.5; low disease activity, ≤3.8; inactive disease, ≤1) [28–31], proportions of patients with inactive disease (JIA ACR inactive disease criteria) [32] and clinical remission on treatment (inactive disease for ≥6 months continuously), functional ability using the Childhood HAQ–Disability Index (CHAQ-DI; range, 0–3) [33] and growth measured using height velocity (cm/year).

Statistical analysis

Descriptive statistical analyses were planned. Population PK models previously developed for i.v.-TCZ in sJIA and pJIA were used to delineate the weight-based s.c.-TCZ dose regimens. Subsequently, individual model–computed PK parameters were estimated after data were incorporated from the s.c.-TCZ trials [C_{trough}, area under the concentration-time curve (AUC), and maximum concentration (C_{max}) at steady-state]. Dense sampling after the first s.c.-TCZ dose allowed for characterization of absorption parameters.

At the week 14 interim analysis, a dosing change from Q10D to Q2W was introduced for sJIA patients weighing <30 kg, because the Q10D regimen resulted in exposures higher than those observed with i.v.-TCZ for some patients.

All enrolled patients who received ≥1 dose of s.c.-TCZ were included in the PK/PDy, safety and intention-to-treat analysis populations.

Results

Patients

Among 51 sJIA patients, 44 (86%) completed 52 weeks (Fig. 1A), 4 withdrew for lack of efficacy, 1 withdrew based on the physician's decision (because of persistently low neutrophil counts) and 2 died. Among 52 pJIA patients (Fig. 1B), 46 (89%) completed 52 weeks, 5 withdrew for lack of efficacy and 1 withdrew based on the patient's decision.

Demographic and disease characteristics at baseline were balanced between body weight groups in both studies (Table 1). Four patients were younger than 2 years of age at baseline—three in the sJIA study (aged 17, 19 and 22 months) and one in the pJIA study (aged 23 months). Demographics of TCZ-naive patients with sJIA and pJIA were similar to those in the TCZ-prior groups, except for higher JADAS-71 and CHAQ-DI scores at baseline (Table 1).

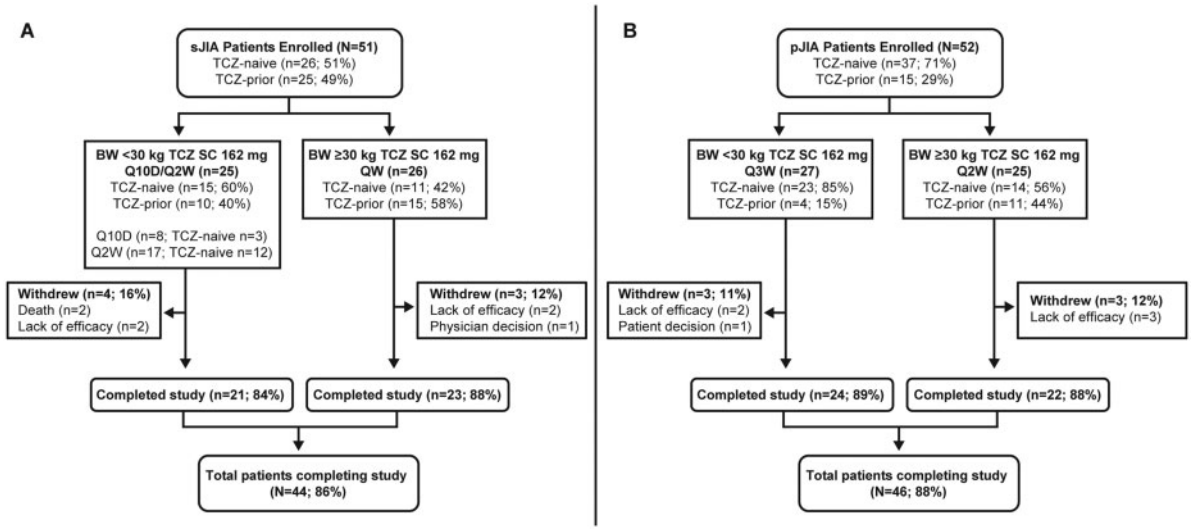
Pharmacokinetics

C_{trough} values reached stable levels around week 12 or 14 in TCZ-naive sJIA and pJIA patients newly initiating s.c.-TCZ. C_{trough} levels were maintained in TCZ-prior patients on switching to s.c.-TCZ.

Median steady-state C_{trough} levels were similar across body weight groups in sJIA patients after dose adjustment to Q2W in the <30-kg group (<30 kg, 64.2 μg/ml; ≥30 kg, 72.4 μg/ml) and in pJIA patients (<30 kg, 13.4 μg/ml; ≥30 kg, 12.7 μg/ml) (Fig. 2, Supplementary Table S1, available at *Rheumatology* online). Among TCZ-naive patients with sJIA, median steady-state C_{trough} (range) was higher in the <30-kg group treated with s.c.-TCZ Q10D [116 (91.8–256.0) μg/ml] than with s.c.-TCZ Q2W [41.4 (12.8–114.0) μg/ml], which led to dose reduction to Q2W in this group after the interim analysis. For pJIA patients, and to a lesser extent sJIA patients, median steady-state C_{max} and overall exposure (AUC) were slightly higher in patients weighing <30 kg than in those weighing ≥30 kg (Fig. 2, Supplementary Fig. S1, Supplementary Table S1, available at *Rheumatology* online). Comparison of exposure after s.c. *vs* i.v. administration indicated that, consistent with initial model predictions, a high percentage (96%; 49/51) of sJIA patients and all (100%) pJIA patients treated with s.c.-TCZ had a steady-state C_{trough} at or above the 5th percentile of that achieved in the i.v.-TCZ trial across the body weight range (Fig. 2). Similarly, 80.4% (41/51) of sJIA patients and 78.8% (41/52) of pJIA patients had steady-state C_{trough} values between the 5th and 95th percentiles of values achieved with i.v.-TCZ. As expected, the C_{max} attained with s.c.-TCZ was lower than that attained with i.v.-TCZ (Fig. 2).

C_{trough} values in the three sJIA patients aged <2 years were at the higher end of the exposure spectrum (above the 53rd percentile of exposure in the <30-kg group) following treatment with s.c.-TCZ, but were within the range of model-predicted exposures in sJIA patients aged ≥2 years (19.5–158 μg/ml).

FIG. 1 Patient disposition in the trial of (A) patients with sJIA and (B) patients with pJIA



Withdrawal by patient: TCZ-naive, $n = 1$. Withdrawal because of lack of efficacy: TCZ-naive, $n = 4$; TCZ-prior, $n = 1$. BW: body weight; Q10D: every 10 days; QW: every week; Q2W: every 2 weeks; TCZ: tocilizumab; pJIA: polyarticular JIA; sJIA: systemic JIA.

Pharmacodynamics

Changes in PDy parameters over time were comparable for TCZ-naive patients initiating treatment with s.c.-TCZ and i.v.-TCZ and remained stable for patients switching from i.v.-TCZ to s.c.-TCZ. Median soluble IL-6R (sIL-6R) serum concentrations increased rapidly in TCZ-naive patients after the first TCZ dose through week 12 and then stabilized between 500 and 800 ng/ml. Among TCZ-prior patients, median sIL-6R concentrations remained stable over time compared with baseline levels. Consistent with TCZ exposures, sIL-6R levels were slightly higher in patients weighing <30 kg than ≥30 kg over the dosing period in both disease populations (Fig. 3). Median IL-6 concentrations stabilized by week 12 (Supplementary Fig. S2, available at *Rheumatology* online). Median CRP levels and ESR decreased rapidly among TCZ-naive patients with s.c.-TCZ and remained within the normal range reported in the i.v.-TCZ studies [14, 15] among TCZ-prior patients (Supplementary Fig. S3, available at *Rheumatology* online).

Exploratory efficacy analysis

JADAS-71 improved in TCZ-naive sJIA and pJIA patients treated with s.c.-TCZ, similar to improvements observed with i.v.-TCZ, indicating that comparable efficacy was achieved with the s.c. and i.v. formulations (Supplementary Fig. S4, available at *Rheumatology* online). In addition, JADAS-71 was maintained in TCZ-prior patients (Fig. 4; Supplementary Fig. S4, available at *Rheumatology* online), indicating that patients could switch from i.v. to s.c. and maintain the same level of efficacy. Among all patients who had efficacy data at week 52, 3 of 43 (7.0%) children with sJIA and 8 of 47 (17.0%) children with pJIA were able to reach a status of moderate disease activity (JADAS-71 3.9–10.5), and 40 of 43 (93.0%) children with sJIA and 35 of 47 (74.5%) children with pJIA were able to reach a status of a low disease activity (≤3.8). By week 52, 68.6% (35/51) of sJIA patients and 63.5% (33/52) of pJIA patients had inactive disease; 52.9% (27/51) of sJIA and 30.8% (16/52) of pJIA patients achieved clinical remission on treatment.

The proportion of patients with sJIA receiving glucocorticoid therapy decreased from 27 of 51 (52.9%) at baseline to 7 of 51 (13.7%) at week 52 and from a mean dose of 2.7 mg/kg/day to 0.6 mg/kg/day, respectively, for patients <30 kg and from 0.3 mg/kg/day to 0.1 mg/kg/day, respectively, for patients ≥30 kg. The proportion of pJIA patients receiving glucocorticoid therapy decreased from 17 of 52 (32.7%) at baseline to 5 of 52 (9.6%) at week 52 and from a mean dose of 0.2 mg/kg/day to 0 mg/kg/day, respectively, for patients <30 kg and from 0.2 mg/kg/day to 0.1 mg/kg/day, respectively, for patients ≥30 kg (Supplementary Table S2, available at *Rheumatology* online). Exploratory analysis of growth showed that the distribution of height velocities was consistent with World Health Organization normative values (Supplementary Fig. S5, available at *Rheumatology* online) and in line with observations for pJIA and sJIA with i.v.-TCZ [34, 35].

Safety

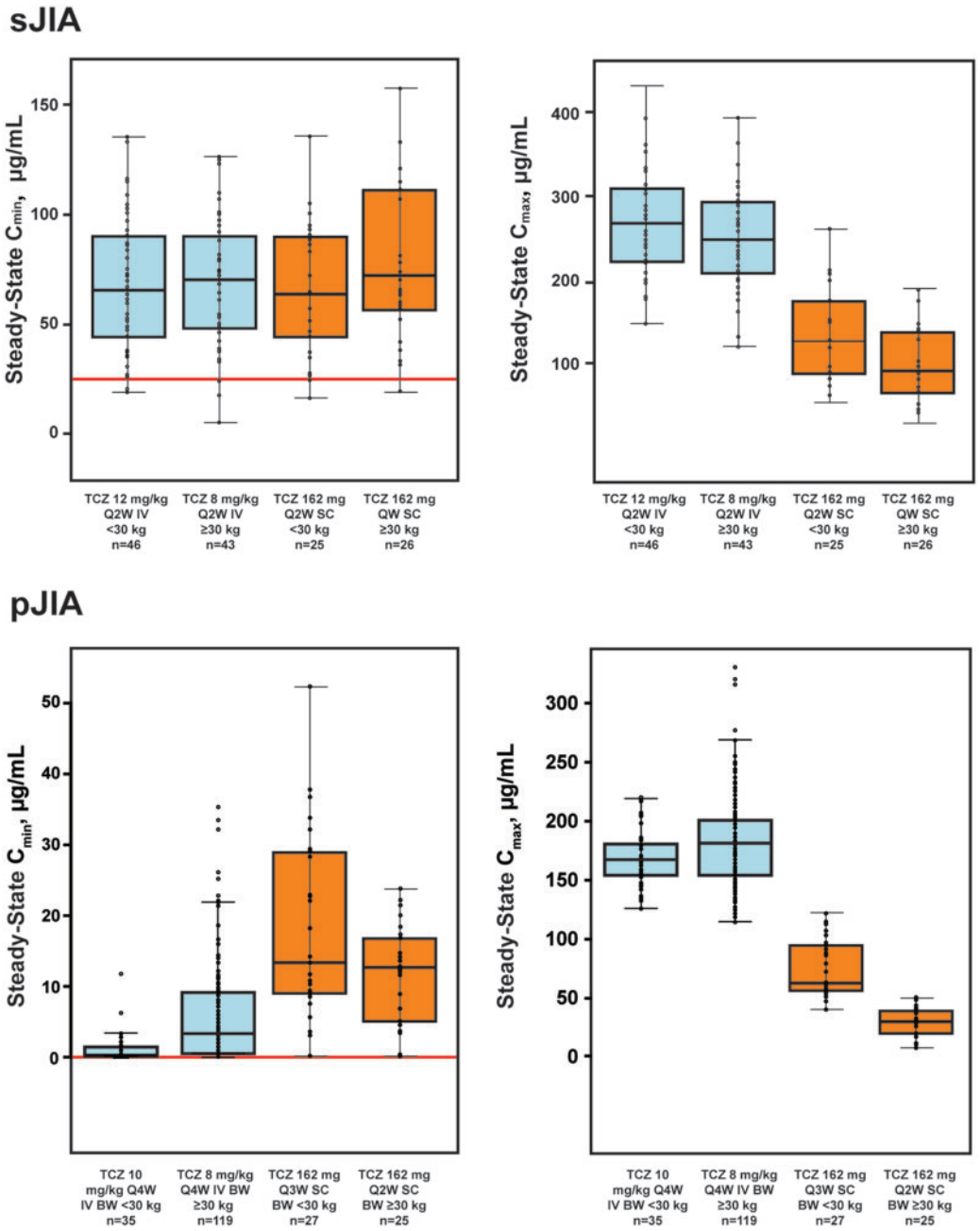
A total of 46.7 patient-years (PY) of follow-up for sJIA patients was available for safety assessment: 23.0 PY in the <30-kg group and 23.8 PY in the ≥30-kg group. Total follow-up in the pJIA study was 50.4 PY overall: 26.6 PY for the <30-kg group and 23.8 PY for the ≥30-kg group.

Table 1 Baseline demographics and disease characteristics of patients with sJIA and patients with pJIA

Characteristic	sJIA						pJIA					
	TCZ-naive $n=26$		TCZ-prior $n=25$		All TCZ $n=51$		TCZ-naive $n=37$		TCZ-prior $n=15$		All TCZ $n=52$	
	<30 kg Q10D/Q2W $n=15$	≥30 kg QW $n=11$	<30 kg Q10D/Q2W $n=10$	≥30 kg QW $n=15$	<30 kg Q10D/Q2W $n=25$	≥30 kg QW $n=26$	<30 kg Q3W $n=23$	≥30 kg Q2W $n=14$	<30 kg Q3W $n=4$	≥30 kg Q2W $n=11$	<30 kg Q3W $n=27$	≥30 kg Q2W $n=25$
Age, years, mean (S.D.)	5.2 (3.0)	13.1 (3.2)	4.9 (3.6)	13.5 (3.2)	5.1 (3.2)	13.3 (3.2)	5.3 (2.1)	14.9 (2.2)	6.8 (1.0)	12.7 (2.9)	5.5 (2.1)	13.9 (2.7)
Females, *n* (%)	7 (46.7)	6 (54.5)	6 (60.0)	10 (66.7)	13 (52.0)	16 (61.5)	14 (60.9)	10 (71.4)	4 (100.0)	8 (72.7)	18 (66.7)	18 (72.0)
Weight, kg, mean (S.D.)	19.1 (5.4)	52.2 (14.3)	18.1 (6.4)	51.3 (12.8)	18.7 (5.7)	51.7 (13.2)	19.2 (4.9)	60.4 (15.1)	22.2 (1.3)	51.9 (15.3)	19.7 (4.7)	56.7 (15.5)
No. of active joints, mean (S.D.)	11.6 (11.6)	6.6 (8.1)	1.3 (1.8)	1.2 (2.2)	7.5 (10.3)	3.5 (6.0)	9.4 (7.5)	11.4 (8.5)	1.3 (1.9)	7.0 (11.2)	8.2 (7.5)	9.5 (9.8)
CHAQ-DI score, mean (S.D.)	1.28 (0.93)	0.78 (1.00)	0.28 (0.42)	0.45 (0.77)	0.88 (0.90)	0.59 (0.88)	0.95 (0.66)	0.88 (0.70)	0.50 (0.51)	0.59 (0.73)	0.88 (0.65)	0.76 (0.72)
JADAS-71 score, mean (S.D.)	23.6 (15.6)	15.9 (12.4)	3.2 (3.3)	3.5 (5.2)	15.5 (15.8)	8.7 (10.8)	19.7 (9.8)	21.0 (9.9)	5.9 (7.1)	11.4 (14.6)	17.6 (10.6)	16.8 (12.9)
Concurrent MTX use, *n* (%)	8 (53.3)	5 (45.5)	5 (50.0)	9 (60.0)	13 (52.0)	14 (53.8)	18 (78.3)	7 (50.0)	3 (75.0)	8 (72.7)	21 (77.8)	15 (60.0)
Concurrent glucocorticoid use, *n* (%)[a]	14 (93.3)	8 (72.7)	6 (60.0)	4 (26.7)	20 (80.0)	12 (46.2)	11 (47.8)	6 (42.9)	0	6 (54.5)	11 (40.7)	12 (48.0)
Previous biologic use, *n* (%)	4 (26.7)	8 (72.7)	10 (100.0)	15 (100.0)	14 (56.0)	23 (88.5)	6 (26.1)	10 (71.4)	4 (100)	11 (100)	10 (37.0)	21 (84.0)

CHAQ-DI: Childhood HAQ–Disability Index; JADAS-71: Juvenile Arthritis DAS including 71 joints; pJIA: polyarticular JIA; Q10D: every 10 days; QW: every week; Q2W: every 2 weeks; Q3W: every 3 weeks; sJIA systemic JIA; TCZ: tocilizumab. [a]Included all prior and concomitant use.

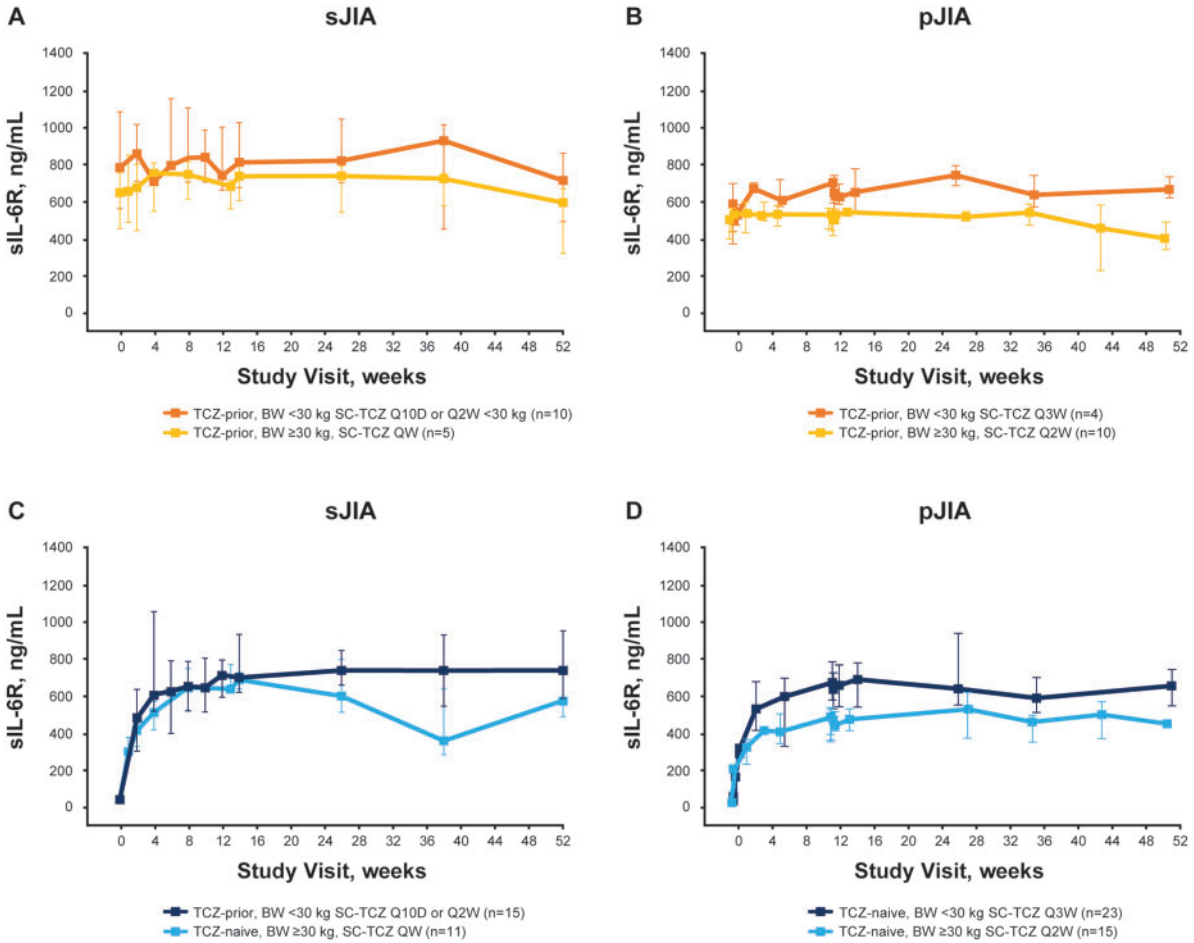
FIG. 2 Model-computed median steady-state C_{min} and C_{max} from s.c. dosing *vs* i.v. dosing



Median values are designated by black lines in the centres of the boxes. Boxes indicate the IQR. Whiskers represent 1.5 × IQR. Horizontal red line denotes the model-computed 5th percentile from the i.v.-TCZ trials. The number of i.v.-TCZ sJIA patients includes all patients randomly assigned to TCZ in part 1 of the i.v.-TCZ trial and any patient who escaped from placebo to TCZ in part 1 for whom a PK sample was available. BW: body weight; C_{max}: maximum concentration; C_{min}: minimum concentration; IQR: interquartile range; PK: pharmacokinetic; QW: every week; Q2W: every 2 weeks; Q3W: every 3 weeks; TCZ: tocilizumab; sJIA: systemic JIA.

Most AEs in both studies were mild or moderate in intensity and were considered unrelated to TCZ treatment. A higher AE rate was observed in patients in the ≥30-kg body weight group than the <30-kg group in both studies: 1378.7/100 PY (95% CI, 1233.5–1536.3) *vs* 1015.3/100 PY (889.1–1154.3) in sJIA patients and 944.2/100 PY (824.8–1076.0) *vs* 680.5/100 PY (584.9–787.1) in pJIA patients. Similar AE rates were observed in TCZ-naive patients and TCZ-prior patients with sJIA (1196.2/100 PY and 1205.0/100 PY), whereas in pJIA

FIG. 3 sIL-6R concentration-time profiles with s.c.-TCZ treatment of TCZ-prior (A, B) and TCZ-naive (C, D) patients



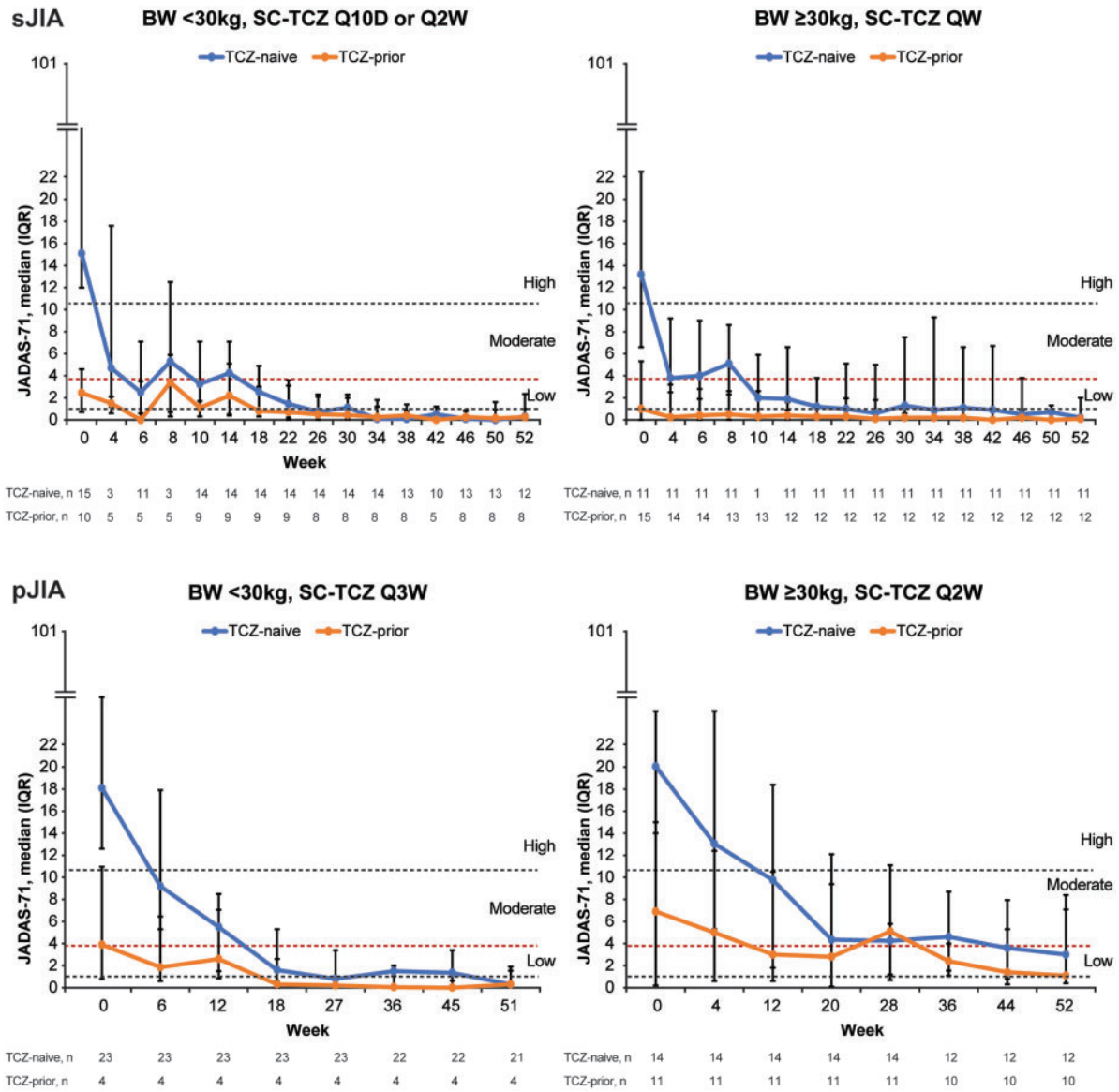
Data are shown as median (IQR) values. Error bars = IQR. BW: body weight; IQR: interquartile range; Q10D: every 10 days; QW: every week; Q2W: every 2 weeks; Q3W: every 3 weeks; sIL-6R: serum IL-6 receptor; TCZ: tocilizumab.

patients, the AE rate was higher in TCZ-naive patients than in TCZ-prior patients (876.1/100 PY *vs* 631.0/100 PY). The most common AEs were from the infections and infestations system organ class (Table 2), reported by a higher proportion of patients in the <30-kg group than in the ≥30-kg group (88% *vs* 69.2%, respectively, for sJIA; 74.1% *vs* 64%, respectively, for pJIA). Overall, nine SAEs occurred in seven sJIA patients (five serious infections, two sJIA flares, vertigo and pulmonary hemorrhage), and four SAEs occurred in three pJIA patients (croup, varicella, worsening of anorexia and arthralgia) (Supplementary Data S4, available at *Rheumatology* online). AEs and SAEs among the three sJIA patients who were aged <2 years at the time of enrolment were consistent with those observed in the older sJIA patients. No serious or clinically significant hypersensitivity reactions and no cases of anaphylaxis or macrophage activation syndrome, gastrointestinal perforations, serious hepatic AEs, malignancies, serious myocardial infarctions, opportunistic infections or serious strokes were reported during this study.

Two patients with sJIA died, both in the <30-kg group. Both deaths were considered related to TCZ. A TCZ-naive patient had oral candidiasis and pneumonia and died of pulmonary hemorrhage on day 15 after receiving a single TCZ dose on day 1, and another patient died of suspected sepsis on day 262. Both patients were receiving concomitant steroids and other medications (Supplementary Data S4, available at *Rheumatology* online). No deaths occurred during the pJIA study.

The AE profile for s.c.-TCZ was comparable with that observed with the i.v.-TCZ regimens in sJIA and pJIA (Supplementary Table S3, available at *Rheumatology* online) except for injection site reactions (ISRs), which are applicable only for patients receiving s.c.-TCZ. Overall, 41.2% of sJIA patients treated with s.c.-TCZ reported ≥1 ISR (20% of patients weighing <30 kg, 61.5% of patients weighing ≥30 kg), as did 28.8% of pJIA patients (14.8% of patients weighing <30 kg, 44.0% of patients weighing ≥30 kg). All ISRs were considered non-serious, and none required withdrawal from treatment. There

FIG. 4 JADAS-71 over time for sJIA and pJIA patients treated with s.c.-TCZ



Data are shown as median (IQR) valuesData points at weeks 4 and 8 for the <30kg group (left-hand sJIA panel) include only those for patients receiving Q10D dosing. Horizontal dashed lines represent inactive disease (JADAS-71 < 1.0), low disease activity (≤3.8), moderate disease activity (3.9–10.5) and high disease activity (>10.5). BW: body weight; IQR: interquartile range; JADAS-71: Juvenile Arthritis DAS including 71 joints; pJIA: polyarticular JIA; Q10D: every 10 days; QW: every week; Q2W: every 2 weeks; Q3W: every 3 weeks; s.c.-TCZ: subcutaneous tocilizumab; sJIA: systemic JIA; TCZ: tocilizumab.

were no serious or clinically significant hypersensitivity reactions (defined as hypersensitivity reactions leading to withdrawal) or confirmed anaphylaxis (Supplementary Data S4, available at *Rheumatology* online). Laboratory abnormalities were consistent with those expected in children treated with TCZ—most commonly, decrease in neutrophil count (sJIA, 54.9%; pJIA, 42.3%; all grade ≤3), elevated alanine aminotransferase levels (sJIA, 33.3%; pJIA 38.5%; all grade ≤3 except one grade 4 for sJIA) and elevated aspartate aminotransferase levels (sJIA, 23.5%; pJIA 25.0%; all grade ≤3) (Supplementary Data S5, available at *Rheumatology* online).

No patients with sJIA developed detectable anti-TCZ antibodies. Among pJIA patients, three who were TCZ-naive (one weighing <30 kg, two weighing ≥30 kg) developed anti-TCZ antibodies after baseline, but not of the immunoglobulin E isotype. One of these patients was withdrawn because of lack of efficacy (treating physician decision). One patient who developed anti-TCZ antibodies after baseline had injection site

Table 2 Safety profile of s.c.-TCZ in patients with sJIA and patients with pJIA

Safety outcomes	sJIA						pJIA					
	<30 kg Q10D/Q2W *n* = 25		≥30 kg QW *n* = 26		All TCZ *n* = 51		<30 kg Q3W *n* = 27		≥30 kg Q2W *n* = 25		All TCZ *n* = 52	
	TCZ-naive *n* = 15	TCZ-prior *n* = 10	TCZ-naive *n* = 11	TCZ-prior *n* = 15	TCZ-naive *n* = 26	TCZ-prior *n* = 25	TCZ-naive *n* = 23	TCZ-prior *n* = 4	TCZ-naive *n* = 14	TCZ-prior *n* = 11	TCZ naive *n* = 37	TCZ-prior *n* = 15
PY of follow-up	13.9	9.1	11.2	12.6	25.1	21.7	22.6	4.0	13.3	10.5	35.8	14.6
Patients with ≥1 AE, *n* (%)	15 (100)	10 (100)	11 (100)	14 (93.3)	26 (100)	24 (96)	21 (91.3)	4 (100)	13 (92.9)	10 (90.9)	34 (91.9)	14 (93.3)
Total AEs, *n*	131	102	169	159	300	261	167	14	147	78	314	92
Patients with ≥1 SAE, *n* (%)	3 (20)	2 (20)	1 (9.1)	1 (6.7)	4 (15.4)	3 (12)	1 (4.3)	0	1 (7.1)	1 (9.1)	2 (5.4)	1 (6.7)
AEs by system organ class, *n* (%)[a]												
Infections and infestations[b]	12 (80)[e]	10 (100)	9 (81.8)	9 (60)	21 (80.8)	19 (76)	18 (78.3)	2 (50)	9 (64.3)	7 (63.6)	27 (73)	9 (60)
Musculoskeletal and CTDs	3 (20)	4 (40)	3 (27.3)	4 (26.7)	6 (23.1)	8 (32)	11 (47.8)	0	7 (50.0)	5 (45.5)	18 (48.6)	5 (33.3)
Gastrointestinal disorders[c]	5 (33.3)	6 (60)	3 (27.3)	9 (60)	8 (30.8)	15 (60)	8 (34.8)	2 (50.0)	7 (50.0)	4 (36.4)	15 (40.5)	6 (40.0)
General disorders and administrative site conditions	5 (33.3)	4 (40)	6 (54.5)	12 (80)	11 (42.3)	16 (64)	4 (17.4)	2 (50.0)	9 (64.3)	5 (45.5)	13 (35.1)	7 (46.7)
Respiratory, thoracic and mediastinal disorders	9 (60)	4 (40)	6 (54.5)	6 (40)	15 (57.7)	10 (40)	10 (43.5)	1 (25.0)	1 (7.1)	6 (54.5)	11 (29.7)	7 (46.7)
Skin and s.c. tissue disorders	5 (33.3)	3 (30)	6 (54.5)	1 (6.7)	11 (42.3)	4 (16)	5 (21.7)	0	5 (35.7)	2 (18.2)	10 (27.0)	2 (13.3)
Nervous system disorders	0	0	2 (18.2)	5 (33.3)	2 (7.7)	5 (20.0)	2 (8.7)	0	5 (35.7)	3 (27.3)	7 (18.9)	3 (20.0)
Psychiatric disorders[d]	0	0	1 (9.1)	0	1 (3.8)	0	3 (13.0)	1 (25.0)	3 (21.4)	1 (9.1)	6 (16.2)	2 (13.3)
Blood and lymphatic system disorders	5 (33.3)	3 (30)	4 (36.4)	6 (40)	9 (34.6)	9 (36)	3 (13.0)	0	1 (7.1)	0	4 (10.8)	0
Injury, poisoning and procedural complications	3 (20)	4 (40)	5 (45.5)	3 (20)	8 (30.8)	7 (28)	3 (13.0)	1 (25.0)	2 (14.3)	1 (9.1)	5 (13.5)	2 (13.3)
Investigations	2 (13.3)	3 (30)	2 (18.2)	1 (6.7)	4 (15.4)	4 (16)	4 (17.4)	0	2 (14.3)	0	6 (16.2)	0

Multiple occurrences of the same event in a patient were counted once. AE: adverse event; BW: body weight; pJIA: polyarticular JIA; PY: patient years; Q10D: every 10 days; QW: every week; Q2W: every 2 weeks; Q3W: every 3 weeks; SAE: serious adverse event; sJIA: systemic JIA; SOC: system organ class; TCZ: tocilizumab. [a]SOC included if all-grade AEs within that SOC occurred in ≥15% of sJIA patients or pJIA patients overall. [b]The most common infections (≥10% of all patients) were nasopharyngitis (34.6%), gastroenteritis (11.5%) and upper respiratory tract infections (9.6%) in pJIA patients and viral upper respiratory tract infection (25.5%), upper respiratory tract infection (21.6%) and rhinitis (11.8%) in sJIA patients. [c]No patients experienced gastrointestinal perforations. [d]The most common psychiatric disorder in pJIA patients was insomnia (four TCZ-naive patients). Others included depression (one TCZ-naive patient) and fear of injections (one patient who previously received TCZ). [e]One patient was receiving QW dosing at the time of infection (serious sepsis infection that was fatal) after a body weight increase to ≥30 kg.

hematomas on days 2 and 16. The other two patients did not experience ISRs.

Discussion

Bridging of PK and PDy to efficacy data is recognized by the US Food and Drug Administration (FDA) [36] and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [37] to support new dose regimens, new dosage forms and new formulations and routes of administration based on known exposure–response relationships from existing clinical trial data as particularly relevant for children. In the s.c.-TCZ trials, 162 mg QW dosing for sJIA patients weighing ≥30 kg (162 mg Q2W for patients <30 kg) and Q2W dosing for pJIA patients weighing ≥30 kg (162 mg Q3W for patients <30 kg) provided TCZ exposures similar to those of approved i.v.-TCZ regimens and resulted in comparable PDy, safety and exploratory efficacy. Based on these data, the FDA and the European Medicines Agency approved these s.c. dosing regimens for the treatment of sJIA and pJIA [38, 39].

A relationship between TCZ predose concentration (C_{trough} or C_{min}, as a measure of exposure) and efficacy has been established for patients with sJIA (data on file) and patients with pJIA [40]. Evaluation and comparison of TCZ exposure after s.c. administration formed the basis of bridging to the pivotal i.v.-TCZ trials in sJIA or pJIA. Consistent with comparable exposures, PDy responses measured by changes in sIL-6R, IL-6, CRP and ESR were comparable with those observed for i.v.-TCZ regimens. The increase observed in serum sIL-6R is consistent with the formation of sIL-6R/TCZ immune complexes [41]. Some measures of TCZ exposure, and correspondingly sIL-6R levels, were slightly higher in the <30-kg group but had no effect on safety or efficacy. The s.c.-TCZ trials confirmed that starting s.c.-TCZ in sJIA or pJIA patients previously treated with i.v.-TCZ can be achieved safely and effectively with the first s.c.-TCZ dose delivered when the next i.v.-TCZ dose is due.

The safety profile of s.c.-TCZ was consistent with that observed with the i.v.-TCZ regimen for sJIA and pJIA patients [14, 15]. The most common AEs were infections, consistent with the safety profile for TCZ. No new types of AE were observed except for ISRs (consistent with s.c. administration). ISR rates of 291.0/100 PY in sJIA patients and 93.2/100 PY in pJIA patients with s.c.-TCZ were higher than those observed in s.c.-TCZ trials in adult RA patients (11.5–26.1/100 PY) [18, 42] (data on file). Fewer patients in the <30-kg groups (sJIA 20%, pJIA 14.8%) than in the ≥30-kg groups (sJIA 61.5%, pJIA 44.0%) reported ISRs, possibly because of a more limited ability of younger patients to articulate certain ISR symptoms. Consistent with previous observations, there was a low incidence of anti-drug antibodies among pJIA patients and none among sJIA patients. Anti-drug antibodies in pJIA patients did not negatively affect the clinical effectiveness of TCZ. Two patients died in the s.c.-TCZ sJIA trial because of complications following serious infections compared with one death from suspected pneumothorax observed over a similar treatment duration in the i.v.-TCZ sJIA trial [14]; none died in the i.v.-TCZ pJIA trial [15]. Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive therapies, including TCZ, highlighting the vigilance required for timely detection and treatment.

Given the similar PK/PDy results for s.c.-TCZ *vs* i.v.-TCZ, comparable efficacy can be expected. Patients newly initiating TCZ therapy had efficacy responses with s.c.-TCZ comparable with those observed in i.v.-TCZ sJIA and pJIA studies, and disease control was maintained for patients who switched from i.v.-TCZ to s.c.-TCZ at study entry and began s.c. injections when the next i.v.-TCZ dose was due. Safety assessment is ongoing in patients with sJIA or pJIA treated with s.c.-TCZ in a long-term extension study that includes ≤5 years of s.c.-TCZ treatment (ClinicalTrials.gov, NCT02165345).

The design of the s.c.-TCZ studies in patients with sJIA and pJIA allowed for robust confirmation of optimal s.c.-TCZ dosing regimens of the s.c. formulation. Eligibility criteria were similar to those of the i.v.-TCZ studies, enabling comparison for confirmation of the dosing strategy and of PK, PDy, safety and efficacy. This meant fewer patients had to undergo the clinical trial procedure, which accelerated the approval and subsequent availability of the s.c.-TCZ formulation compared with a traditional phase 3 trial approach. Limiting the number of TCZ-prior patients to <50% of the total population allowed more precise estimation of PK absorption parameters and determination of the onset of PDy effects after s.c. administration during collection of clinical data for patients switching from i.v.-TCZ to s.c.-TCZ.

Both studies had limitations. The number of patients across the body weight spectrum (at individual ages) might have been too small to enable detection of potentially important immunogenicity and safety differences between s.c.-TCZ and i.v.-TCZ. Other limitations include sparse data for children <2 years ($n = 3$, sJIA; $n = 1$, pJIA), the open-label nature of s.c.-TCZ administration and the lack of statistical comparisons (all comparisons were between-study and descriptive).

In conclusion, appropriate s.c.-TCZ dosing regimens were successfully identified from studies in patients with sJIA or pJIA that bridged to data from studies of i.v.-TCZ. The overall benefit/risk profile for s.c.-TCZ was favourable and comparable with that for i.v.-TCZ in patients with sJIA and in patients with pJIA. These findings highlight the ability of PK/PDy bridging to provide a path towards regulatory approval of agents for the treatment of paediatric patients.

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Data availability statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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