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Original article

Open-label phase 3 study of intravenous golimumab in patients with polyarticular juvenile idiopathic arthritis

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Abstract

Objectives. To assess efficacy, pharmacokinetics (PK) and safety of intravenous (i.v.) golimumab in patients with polyarticular-course JIA (pc-JIA).

Methods. Children aged 2 to <18 years with active pc-JIA despite MTX therapy for ≥2 months received 80 mg/m^2 golimumab at weeks 0, 4, then every 8 weeks through week 52 plus MTX weekly through week 28. The primary and major secondary endpoints were PK exposure and model-predicted steady-state area under the curve (AUC_{ss}) over an 8-week dosing interval at weeks 28 and 52, respectively. JIA ACR response and safety were also assessed.

Results. In total, 127 children were treated with i.v. golimumab. JIA ACR 30, 50, 70, and 90 response rates were 84%, 80%, 70% and 47%, respectively, at week 28 and were maintained through week 52. Golimumab serum concentrations and AUC_{ss} were 0.40 μg/ml and 399 μg · day/ml at week 28. PK exposure was maintained at week

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CLINICAL SCIENCE

52. Steady-state trough golimumab concentrations and AUC_{ss} were consistent across age categories and comparable to i.v. golimumab dosed 2 mg/kg in adults with rheumatoid arthritis. Golimumab antibodies and neutralizing antibodies were detected via a highly sensitive drug-tolerant assay in 31% (39/125) and 19% (24/125) of patients, respectively. Median trough golimumab concentration was lower in antibody-positive *vs* antibody-negative patients. Serious infections were reported in 6% of patients, including one death due to septic shock.

Conclusion. Body surface area-based dosing of i.v. golimumab was well tolerated and provided adequate PK exposure for clinical efficacy in paediatric patients with active pc-JIA.

ClinicalTrials.gov number NCT02277444

Key words: golimumab, intravenous, juvenile idiopathic arthritis, pharmacokinetics, tumour necrosis factor alpha

Rheumatology key messages

- i.v. golimumab 80 mg/m^2 every 8 weeks provided adequate PK exposure in children with pc-JIA.
- i.v. golimumab generally reduced clinical signs and symptoms in children with pc-JIA through week 52.
- i.v. golimumab was generally well tolerated in children with pc-JIA through week 52.

Introduction

JIA, the most common rheumatic disease in children, is diagnosed with onset of arthritis before 16 years of age, persistent objective arthritis for ≥6 weeks, and elimination of other causes of chronic arthritis in children [1]. Treatment of polyarticular course JIA (pc-JIA) includes NSAIDs, intra-articular or systemic glucocorticoids as bridge therapy, and synthetic (s)-DMARDs [2–21]. Children who do not achieve adequate disease control with these agents may require treatment with biologic (b)-DMARDs or, possibly, small molecules.

Golimumab (Janssen Biotech, Inc., Horsham, PA, USA) is a fully human monoclonal antibody that inhibits TNFα. Subcutaneous (s.c.) and intravenous (i.v.) golimumab are effective in RA, PsA and ankylosing spondylitis (AS) in adults. In a previous study in children with active pc-JIA, s.c. golimumab was well tolerated and, although the primary endpoint was not met, clinically meaningful improvement was achieved [15].

Here we report the pharmacokinetics (PK), efficacy and safety profile of i.v. golimumab through 52 weeks of treatment in children with pc-JIA.

Methods

Patients and study design

This was a phase 3, open-label, single-arm, international study conducted in 33 centres in nine countries of the Pediatric Rheumatology Collaborative Study Group (PRCSG) [22] and the Paediatric Rheumatology INternational Trials Organisation (PRINTO) [23]. Eligible patients were 2 to <18 years of age weighing >15 kg at the time of screening and enrolment, with a ≥3-month history of pc-JIA and active arthritis (≥5 active joints) despite MTX (≥10 mg/m^2) treatment for ≥2 months before screening, and onset of disease before their 16th birthday. Pc-JIA could include one of the following categories classified per JIA International League of Associations for Rheumatology (ILAR) classification criteria [24, 25]: extended oligoarticular JIA, RF-positive or RF-negative pc-JIA, systemic JIA with no systemic symptoms for ≥3 months, enthesitis-related arthritis or polyarticular juvenile PsA.

All eligible patients received 80 mg/m^2 golimumab i.v. (maximum single dose of 240 mg, over 30 (10) min) at weeks 0 and 4 and then every 8 weeks (q8w) through week 52 (Supplementary Fig. S1, available at *Rheumatology* online). Body surface area (BSA) was calculated at each visit, and the dose was adjusted as needed to maintain 80 mg/m^2. Commercial MTX was administered weekly at least through week 28 at the same dosage as at study entry (10–30 mg/m^2 for BSA <1.67 m^2 or ≥15 mg for BSA ≥1.67 m^2) [4–6]. After week 28, MTX, other DMARDs, glucocorticoids and NSAIDs could be changed/added. Patients who completed the study could enter the ongoing long-term extension phase.

Patients had to be medically stable and could not have had active uveitis ≤3 months before screening or a major concurrent medical condition. Patients with evidence of active tuberculosis were excluded. Patients with latent tuberculosis were eligible if they were currently receiving treatment.

If the patient was using glucocorticoids (≤10 mg/day or 0.20 mg/kg/day, whichever was less, for prednisone equivalent) or NSAIDs, the dose must have been stable for ≥2 weeks before the first i.v. golimumab administration or screening, respectively. Up to 30% of patients could have prior exposure to ≤2 anti-TNF agents. Patients treated with a b-DMARD or small molecule therapeutic before first i.v. golimumab administration observed specific washout periods. Cytotoxic agents were prohibited.

An independent ethics committee or institutional review board approved the study protocol for each site, and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements. ClinicalTrials.gov registration number is NCT02277444. Patients who were aged ≥7 years gave assent, and parents, a legal guardian or a legally acceptable representative gave written informed consent.

Study assessments

Serum golimumab concentrations were measured at weeks 0, 4, 8, 12, 20, 28 and 52 using a validated, specific and sensitive method [26]. Pre-infusion and post-infusion samples were drawn at weeks 0, 4 and 12, and an additional random population PK sample was drawn any time between weeks 0 and 8 other than weeks 0, 4 and 8 and collected ≥24 h before or after golimumab administration. Pre-infusion samples only were drawn at weeks 8, 20, 28 and 52.

Efficacy assessments included the JIA core set of measures [27] [physician global assessment of overall disease activity (medical doctor (MD) global of disease activity; 0- to 10-cm visual analogue scale (VAS) from 'no arthritis activity' to 'extremely active arthritis') [28], number of joints with active arthritis (swelling or, if no swelling is present, joints with limited range of motion and pain simultaneously), number of joints with limited range of motion, the cross-culturally adapted and validated version of the Childhood HAQ (CHAQ; including parent assessment of overall well-being and pain using VAS (0–10 cm)) [29, 30] and CRP (normal ≤0.287 mg/dl for patients without underlying inflammatory disease)], and morning stiffness duration.

Safety assessments were performed at every visit and included routine laboratory evaluations. Any adverse events (AEs) were coded as per the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. Antibodies to golimumab were evaluated in serum samples collected at weeks 0, 4, 8, 12, 28 and 52 using a validated, highly sensitive drug-tolerant enzyme immunoassay method [31]. Patients with samples classified as anti-drug antibody (ADA) positive [treatment boosted (increased titre if baseline sample was ADA positive) or treatment induced] at any time after their first golimumab administration through week 52 were classified as ADA positive. Patients with baseline samples classified as ADA positive and without increased titre after treatment were classified as ADA negative. The presence of anti-nuclear antibodies (ANAs)/anti-double stranded DNA (dsDNA) antibodies was evaluated in serum samples collected at baseline, week 24 and week 52.

Study endpoints

The primary endpoints of this study were golimumab trough concentrations and model-predicted steady-state area under the curve (AUC_{ss}) over an 8-week dosing interval (from population PK modelling and simulation) at week 28. The major secondary endpoints were golimumab trough concentrations and model-predicted AUC_{ss} at week 52.

Efficacy endpoints included the JIA ACR 30, 50, 70 and 90 responses (i.e. 30%, 50%, 70% or 90% improvement from baseline in ≥3 without worsening of ≥30% in >1 of the remaining JIA core measures) [27] calculated against the closest evaluation performed before the first i.v. golimumab administration (week 0); a modified version of JIA ACR inactive disease [i.e. no joints with active arthritis and no active uveitis; no fever, rash, serositis, splenomegaly, hepatomegaly or generalized lymphadenopathy attributable to JIA; normal CRP; MD global ≤5 mm (no active disease); and duration of morning stiffness <15 min]; clinical remission on medication for pc-JIA (i.e. inactive disease at each visit for ≥6 months while on medication) [32, 33]; and Juvenile Arthritis Disease Activity Score counting 71 joints [JADAS 71; cutoff values: >10.5 for high disease activity (HDA), 3.9–10.5 for moderate disease activity, 1.1–3.8 for low disease activity (LDA) and ≤1 for inactive disease (ID)] [28, 34–40].

Statistical analyses

This study followed the recommendation of the Consolidated Standards of Reporting Trials (CONSORT) statement, with results reported for the full analysis set [41]. All patients who received ≥1 golimumab dose were included in the PK (if PK samples were sufficient), efficacy and safety analyses. A population PK analysis with data through week 28 was performed to characterize golimumab PK and identify important covariates in children with pc-JIA. Population PK modelling was used to assess the similarity of adult and paediatric PK. Clearance and volume of distribution were estimated using non-linear mixed-effects modelling (NONMEM). Exposure–response analysis was performed to characterize the relationship between exposure and efficacy. Measures of PK exposure in the paediatric population were compared with those from a previous study in adults with RA who received i.v. golimumab 2 mg/kg at weeks 0, 4 and q8w thereafter [42].

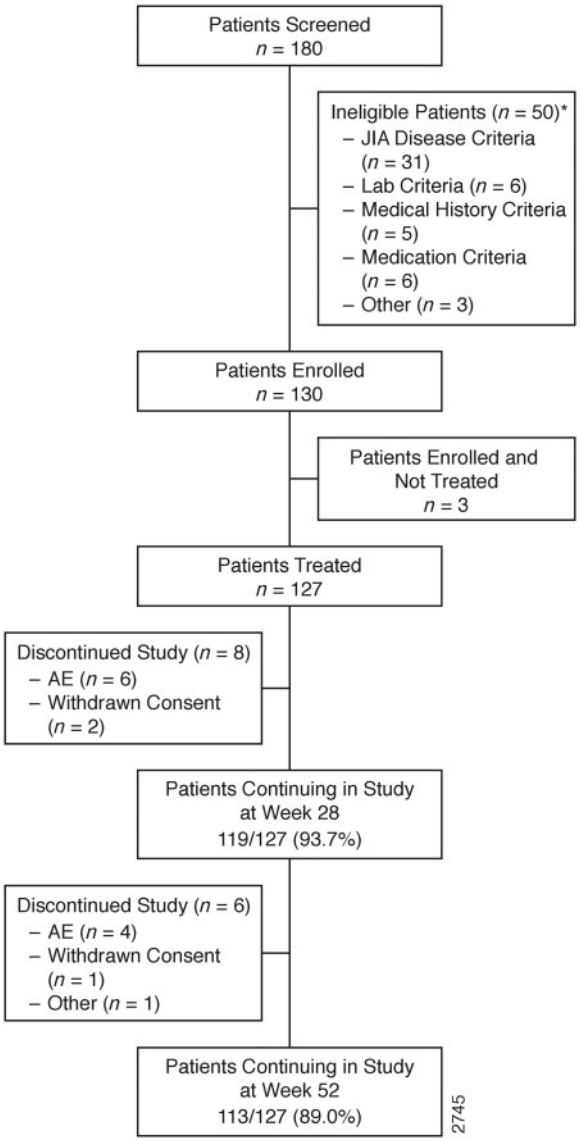
For the analysis of binary composite efficacy endpoints, imputation rules (non-responder imputation for completely missing data and last observation carried forward for missing components) were used for imputing missing data as per the intention-to-treat principle. There was no imputation for continuous endpoints or missing concentration data. No formal hypothesis testing was conducted.

Results

Patient disposition and disease characteristics

Of 180 patients screened, 127 (71%) were enrolled, received ≥1 dose of i.v. golimumab and were included in the full analysis data set (Fig. 1). Of these 127

Fig. 1 Patient disposition



*Adds up to 51 because one patient had more than one reason for ineligibility. AE: adverse event; *n*: number of patients.

patients, 113 (89%) remained in the study through week 52. AEs were the primary reason for discontinuation.

Median age at baseline was 13 years, the majority of patients were female (73%) and white (67%), and median weight was 42.4 kg (Table 1). The majority of patients were classified as RF-negative (43%) and RF-positive (35%) pc-JIA. The most common prior medications were NSAIDs (94%) and systemic glucocorticoids (57%). Overall, 28 patients (22%) had received prior biologic therapy at baseline; of the 25 patients who had received prior anti-TNF therapy, most (80%) had received etanercept. At baseline, 72% of patients were taking NSAIDs, 37% were taking oral glucocorticoids and 10% were taking an s-DMARD other than MTX. At baseline, 121 (99%) patients had HDA as measured by JADAS 71 (Table 2).

Table 1 Baseline demographics, disease characteristics, and prior arthritis treatment

Characteristic	Golimumab (*N* = 127)
Age, median (IQR), years	13.0 (8.0, 15.0)
Female, *n* (%)	93 (73.2)
Race, *n* (%)	
White	85 (66.9)
Other	28 (22.0)
Hispanic or Latino, *n* (%)	63 (49.6)
Weight, median (IQR), kg	42.4 (29.2, 57.0)
BSA, median (IQR), m^2	1.3 (1.0, 1.6)
Duration of disease, median (IQR), years	1.4 (0.5, 4.0)
History of uveitis, *n* (%)	3 (2.4)
ILAR classification, *n* (%)	
Polyarticular RF-negative	54 (42.5)
Polyarticular RF-positive	44 (34.6)
Enthesitis-related arthritis	12 (9.4)
Oligoarticular extended	8 (6.3)
Juvenile PsA	5 (3.9)
Systemic with no systemic symptoms but with polyarticular course	4 (3.1)
ANA positive, *n* (%)	64 (50.4)
Prior joint procedure or injection, *n* (%)	26 (20.5)
Steroid joint injection	25 (96.2)
Other[a]	10 (38.5)
Baseline JIA medications[b]	
MTX, *n* (%)	127 (100)
MTX dose, mean (S.D.), mg/m^2/wk	13.6 (4.5)
s-DMARDs other than MTX, *n* (%)	13 (10.2)
Oral glucocorticoids, *n* (%)	47 (37.0)
Prednisone or equivalent dose, mean (S.D.), mg/kg/day	0.16 (0.1)
NSAIDs, *n* (%)	92 (72.4)
Prior JIA medications[c], *n* (%)	
MTX	127 (100)
s-DMARDs other than MTX[d]	25 (19.7)
Anti-TNF therapy	25 (19.7)
b-DMARDs other than anti-TNF therapy	3 (2.4)
Systemic glucocorticoids	72 (56.7)
NSAIDs	119 (93.7)

[a]Arthrocentesis, arthroscopy (surgical or diagnostic), osteotomy and tendon surgery. [b]Baseline JIA medication is any medication used both before and after the first study agent administration. [c]Prior JIA medication is any medication with a start date before the day of the first study agent administration. [d]Included immunosuppressive agents ciclosporin ($n = 2$) and AZA ($n = 1$). ANA: antinuclear antibody; b-DMARD: biologic DMARD; BSA: body surface area; ILAR: International League of Associations for Rheumatology; IQR: interquartile range; *N*: all treated patients; *n*: number of patients; s-DMARD: synthetic DMARD.

Efficacy

As shown in Table 2, improvement from baseline in the JIA ACR component scores was observed as early as

Table 2 Summary of JIA core set measures and other disease activity parameters ($N = 127$)

Characteristic	Baseline	Week 4	Week 28	Week 52
JIA core set measures, median (IQR)				
MD global of disease activity, 0–10 cm VAS	5.5 (4.5, 6.8)[a]	2.2 (1.0, 3.8)	0.5 (0.1, 1.2)	0.3 (0.0, 1.4)
Parent assessment of overall well-being, 0–10 cm VAS	5.4 (3.3, 6.9)	2.6 (1.1, 5.0)	1.7 (0.3, 4.8)	1.1 (0.2, 4.2)
Number of active joints	14.0 (9.0, 22.0)	6.0 (2.0, 11.0)	1.0 (0.0, 4.0)	0.0 (0.0, 3.0)
Number of joints with limited range of motion	10.0 (4.0, 18.0)	3.0 (0.0, 9.0)	1.0 (0.0, 4.0)	1.0 (0.0, 5.0)
CHAQ, 0–3 score	1.25 (0.8, 1.9)	0.9 (0.4, 1.4)	0.4 (0.0, 1.1)	0.4 (0.0, 1.1)
CRP, mg/dl[b]	0.5 (0.1, 1.1)	0.1 (0.0, 0.3)	0.1 (0.0, 0.7)	0.1 (0.0, 0.6)
Duration of morning stiffness, median (IQR), min	40 (20, 60)	5 (0, 30)	0 (0, 15)	0 (0, 15)
JADAS 71, mean (95% CI)	28.4 (26.1, 30.7)	14.6 (12.4, 16.8)	6.8 (5.2, 8.3)	5.4 (3.9, 6.9)
JADAS 71 high disease activity >10.5, *n* (%)	121 (99.2)	73 (58.9)	23 (20.2)	16 (14.5)
JADAS 71 moderate disease activity 3.9–10.5, *n* (%)	1 (0.8)	32 (25.8)	37 (32.5)	32 (29.1)
JADAS 71 low disease activity 1.1–3.8, *n* (%)	0	15 (12.1)	27 (23.7)	23 (20.9)
JADAS 71 inactive disease ≤1, *n* (%)	0	4 (3.2)	27 (23.7)	39 (35.5)

95% CI is based on normal approximation: mean (1.96) × s.d./$\sqrt{N}$. [a]$n = 122$. [b]Normal is ≤0.287 mg/dl. CHAQ: Childhood HAQ; IQR: interquartile range; JADAS 71: Juvenile Arthritis Disease Activity Score 71 joints evaluated; MD: medical doctor; VAS: visual analogue scale.

week 4 and maintained from week 28 through week 52. At weeks 28 and 52, respectively, median improvement was 92% and 96% for MD global of disease activity, 63% and 70% for parent assessment of overall well-being, 94% and 100% for number of active joints, 89% and 85% for number of joints with limited range of motion, 57% and 63% for physical function by CHAQ, and 53% and 48% for CRP.

Similarly, JIA ACR 30, 50, 70 and 90 responses were observed as early as week 4, with >50% of patients achieving at least JIA ACR 50 (Fig. 2A). At week 28, 70% of patients achieved at least JIA ACR 70 and nearly half (47%) achieved JIA ACR 90; response rates were maintained through week 52. Through weeks 28 and 52, consistently high JIA ACR 30, 50, 70 and 90 response rates were observed across serum trough golimumab concentration quartiles (data not shown). At week 52, the median serum trough golimumab concentration was higher in JIA ACR 30 responders (0.47 μg/ml, $n = 83$) than in non-responders (0.04 μg/ml, $n = 12$); 6 of the 12 non-responders were ADA positive.

JIA ACR inactive disease was achieved by 4% of patients as early as week 4, 29% at week 28 and 34% at week 52 (Fig. 2B). Clinical remission while on medication was achieved by 2% of patients at week 28 and 13% at week 52 (Fig. 2B). Mean improvement from baseline in CHAQ score was observed as early as week 4 (0.34), increased to 0.62 at week 28 and remained stable through week 52 (Fig. 2C). The pattern of improvement was similar for parent assessment of patient pain (Fig. 2C). A decrease in mean JADAS 71 score was observed as early as week 4 and continued through week 52 (Fig. 2D). At week 4, 12% of patients achieved LDA and 3% achieved ID (Table 2). At week 52, 21% of patients achieved LDA and 36% achieved ID.

JIA ACR 30, 50, 70 and 90 response rates among the different pc-JIA subtypes were generally similar to those in the overall population; however, response rates were generally lower in patients with systemic pc-JIA with no systemic symptoms but with polyarticular course (at week 52, 25% had achieved at least JIA ACR 70) and higher in patients with oligoarticular extended or juvenile PsA (at week 52, 88% and 80%, respectively, had achieved at least JIA ACR 70), although these subtypes also had fewer patients (Table 1). JIA ACR and inactive disease response rates tended to be lower in biologic-non-naïve *vs* biologic-naïve patients. At week 52, JIA ACR 30, 50, 70 and 90 and inactive disease response rates were 68%, 68%, 57%, 39% and 25%, respectively, in biologic-non-naïve patients and 78%, 76%, 68%, 52% and 36%, respectively, in biologic-naïve patients.

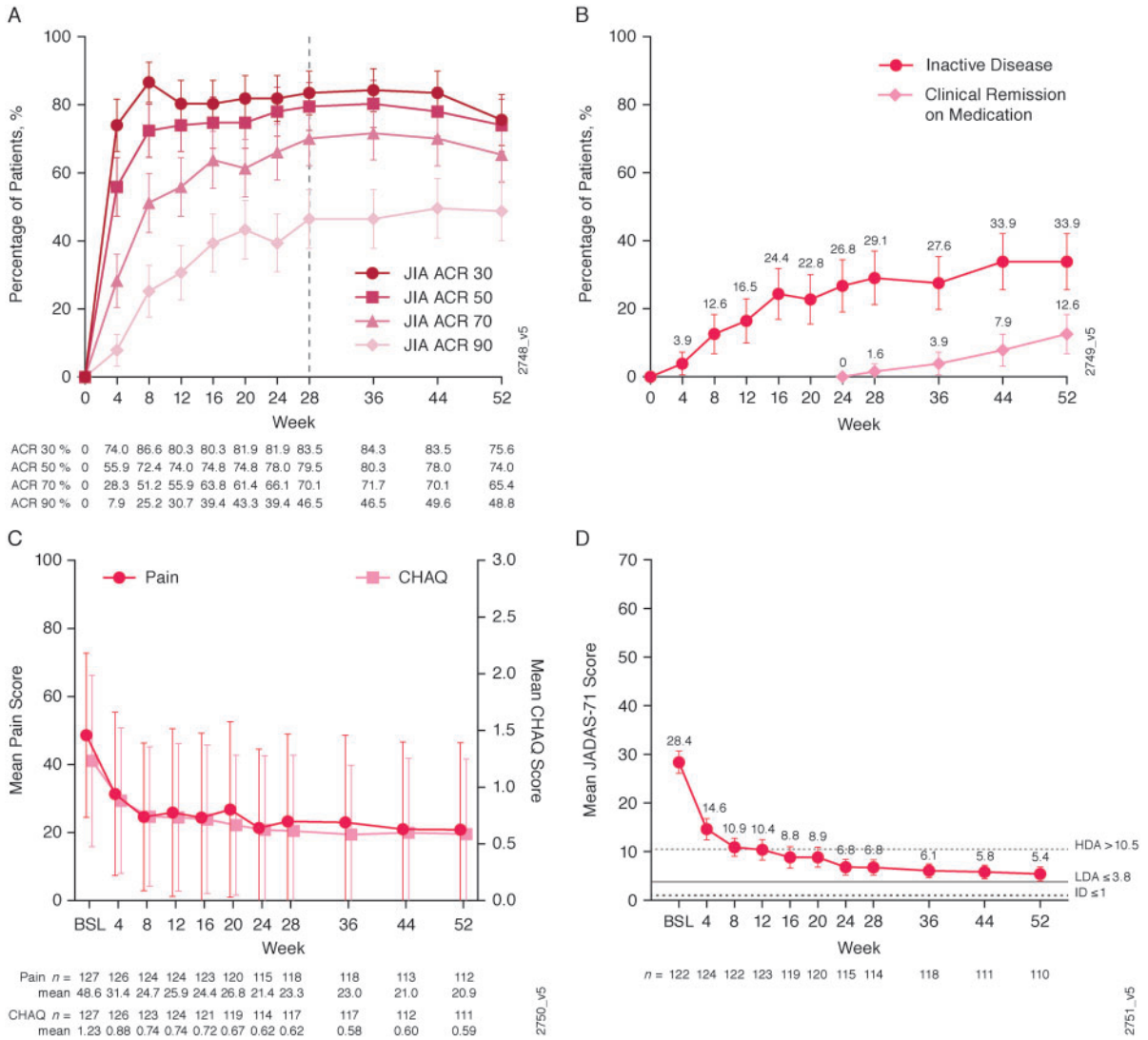
Pharmacokinetics and immunogenicity

Overall, PK exposure in pc-JIA patients after administration of i.v. golimumab was similar to that in the adult RA population (Fig. 3A and B). The overall median steady-state trough golimumab concentration in pc-JIA patients was 0.40 [mean (s.d.): 0.50 (0.43)] μg/ml at week 28 and 0.45 [mean (s.d.): 0.52 (0.48)] μg/ml at week 52. Overall median steady-state trough golimumab concentrations were similar across paediatric age categories at week 28 and similar to the median trough golimumab concentrations at week 36 [0.31 (mean (s.d.): 0.41 (0.52)) μg/ml] in the adult RA population (Fig. 3A) [42]. The observed median trough golimumab concentrations were also similar across body-weight quartiles at week 28.

The population PK model-predicted median overall AUC_{ss} for patients with pc-JIA over an 8-week dosing interval was 399 and 421 μg·day/ml at weeks 28 and 52, respectively. These values were consistent across paediatric age categories (Fig. 3B). The AUC_{ss} values in pc-JIA patients were slightly higher than the AUC_{ss} (248 μg·day/ml) observed in the adult RA population (Fig. 3B).

Through week 52, 39 of 125 (31%) patients with appropriate samples were ADA positive and 24 (19%)

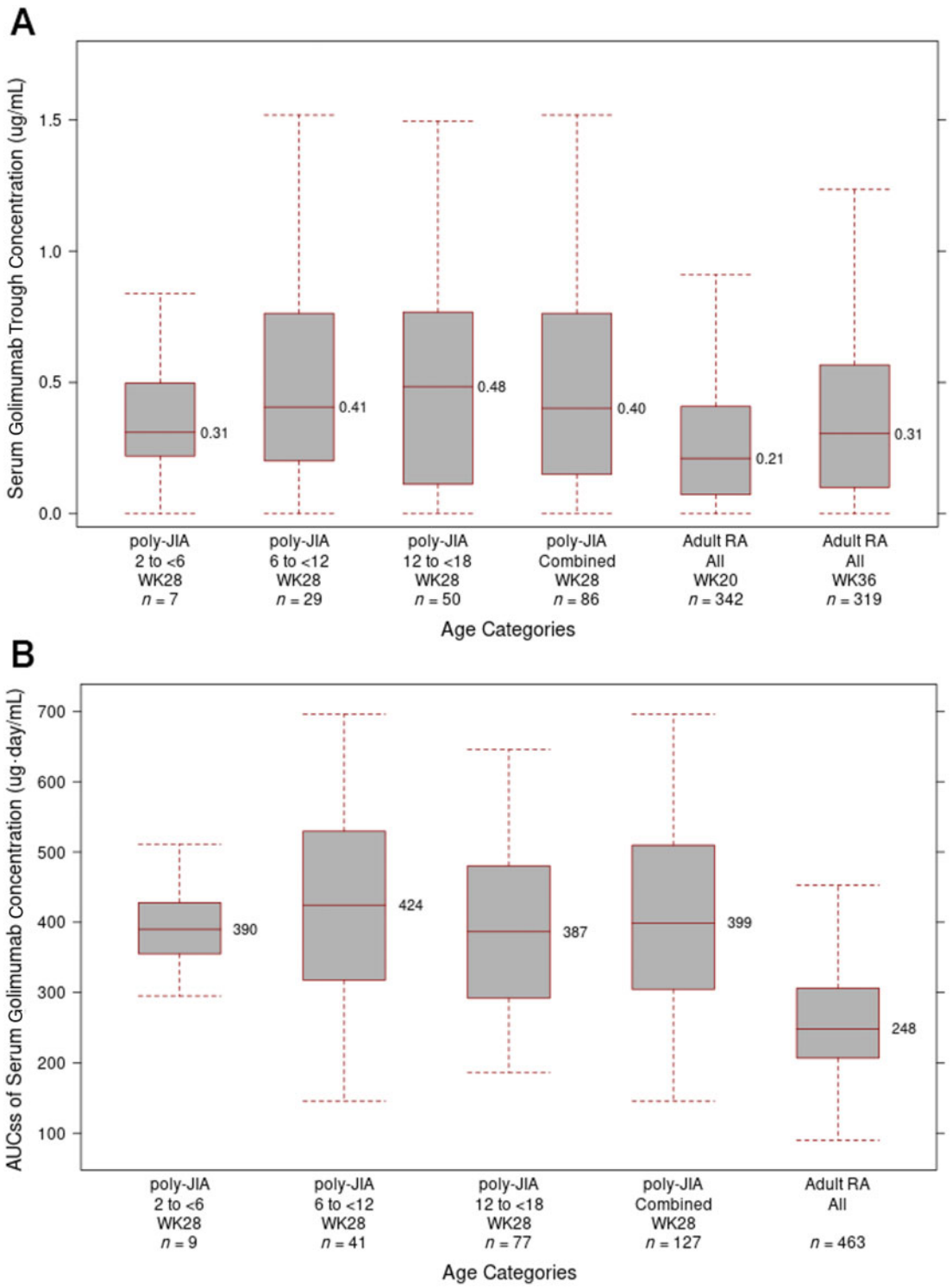
Fig. 2 A–D. Clinical efficacy through week 52



(**A**) Percentage of JIA ACR 30/50/70/90 responders; N=127; missing data were treated per NRI and LOCF. (**B**) Percentage of patients with JIA ACR inactive disease or clinical remission on medication; N=127; clinical remission on medication is inactive disease at each visit for ≥6 months while on medication for pc-JIA (all visits encompassing ≥24 weeks prior had to meet inactive disease criteria). For (**A**) and (**B**), missing data were treated per LOCF and NRI. (**C**) Mean (S.D.) CHAQ and parent assessment of pain scores. (**D**) Mean (95% CI) JADAS 71 scores. 95% CI is based on normal approximation: mean $(1.96) \times$ s.d.$/\sqrt{N}$. (**C**) and (**D**) are based on observed data. BSL: baseline; CHAQ: Childhood HAQ; HDA: high disease activity; ID: inactive disease; JADAS: Juvenile Arthritis Disease Activity Score; LDA: low disease activity; LOCF: last observation carried forward; N: all treated patients; n: number of evaluable patients; NRI: non-responder imputation.

were positive for golimumab neutralizing antibodies (NAbs). Peak titre for antibodies to golimumab was <10 in five patients, ≥10 to <100 in 17 patients, ≥100 to <1000 in 13 patients and ≥1000 in four patients. Select baseline demographic and disease characteristics were generally comparable between ADA- or NAb-positive and ADA- or NAb-negative patients (Supplementary Table S1, available at *Rheumatology* online). NAb-positive patients had a slightly lower baseline weight than the other patient categories (36.9 *vs* 42.2–44.0 kg). In addition, a greater proportion of ADA- and NAb-positive *vs* ADA- and NAb-negative patients were diagnosed with oligoarticular extended pc-JIA (10.3% and 12.5% *vs* 4.7% and 6.7%, respectively), and a greater proportion of NAb-positive patients were diagnosed with polyarticular RF-negative pc-JIA *vs* the other patient categories (41.7% *vs* 26.7% to 35.9%). Median trough golimumab concentration tended to be lower in ADA-

FIG. 3 Observed steady-state serum trough golimumab concentrations (**A**) and model-predicted AUC_{ss} (**B**) at week 28



The horizontal lines within the boxes represent the medians, the lower edges of the boxes represent the first quartile, and the upper edges of the boxes represent the third quartile. Whiskers represent the most extreme observations within the 1.5 × interquartile range. AUC_{ss}: steady-state area under the curve; *n*: number of patients in the population; WK: week.

Table 3 Summary of adverse events through week 52

	Golimumab (*N* = 127)
Average duration of follow-up, weeks	49.8
Average exposure, number of administrations	6.6
Patients who discontinued study agent due to ≥1 AE, *n* (%)	11 (8.7)
Patients with ≥1 AE, *n* (%)	108 (85.0)
Patients with ≥1 severe AE, *n* (%)	5 (3.9)
Patients with ≥1 SAE, *n* (%)	9 (7.1)
AEs per 100 patient-years exposure, *n* (95% CI)	359.6 (326.7, 394.9)
SAEs per 100 patient-years exposure, *n* (95% CI)	8.2 (4.0, 15.1)
Deaths[a]	0
Patients with ≥1 infection, *n* (%)	83 (65.4)
≥1 serious infection, *n* (%)	7 (5.5)
≥1 opportunistic infection, *n* (%)	1 (0.8)
Infections per 100 patient-years exposure, *n* (95% CI)	151.4 (130.3, 174.9)
Serious infection per 100 patient-years exposure, *n* (95% CI)	6.6 (2.8, 13.0)
Patients with ≥1 infusion-related reaction, *n* (%)	3 (2.4)
Patients with ≥1 malignancy[b], *n* (%)	1 (0.8)
Patients with active tuberculosis	0
Positivity for ANA/anti-dsDNA antibodies[c], *n* (%)	13 (25.5)
Common AEs (occurring in ≥5% of patients) by SOC and related Preferred Terms, *n* (%)	
Infections and infestations	85 (66.9)
Upper respiratory tract infection	27 (21.3)
Nasopharyngitis	23 (18.1)
Gastrointestinal disorders	30 (23.6)
Nausea	11 (8.7)
Vomiting	10 (7.9)
Abdominal pain	8 (6.3)
Musculoskeletal and connective tissue disorders	24 (18.9)
JIA	14 (11.0)
Nervous system disorders	20 (15.7)
Headache	14 (11.0)
Investigations	13 (10.2)
Alanine aminotransferase increased	7 (5.5)

[a]One death due to septic shock was reported at week 78. [b]Mycosis fungoides. [c]Newly developed; out of 51 patients who were ANA negative at baseline. AE: adverse event; ANA: antinuclear antibody; anti-dsDNA: anti-double-stranded deoxyribonucleic acid; *N*: all treated patients; *n*: number of patients; SAE: serious adverse event; SOC: system organ class.

positive patients than in ADA-negative patients [0.00 ($n = 32$) *vs* 0.61 μg/ml ($n = 63$) at week 52]. At week 52, JIA ACR 30 and 50 response rates were similar between ADA-positive (74% and 69%, respectively) and ADA-negative (78% for both) patients, whereas JIA ACR 70 and 90 response rates were lower in ADA-positive (54% and 41%, respectively) *vs* ADA-negative (72% and 54%, respectively) patients.

Safety

Through week 52, most patients (85%) experienced ≥1 AE; 7% experienced ≥1 serious AE (SAE) and 9% experienced ≥1 AE that led to discontinuation (Table 3). More than half of treated patients (65%) experienced ≥1 infection, 6% experienced ≥1 serious infection and one experienced a serious opportunistic infection. The proportion of patients with infusion reactions was low (2.3% in ADA-negative and 2.6% in ADA-positive patients); none of the reactions was severe, serious or led to treatment discontinuation; there was no association between the presence of antibodies to golimumab and the occurrence of infusion reactions. No active tuberculosis, demyelinating event, or anaphylactic or serum sickness reactions were reported. Systemic lupus erythematosus, reported in one patient, was considered to be non-serious and not related to golimumab. No deaths were reported through week 52, but one death due to septic shock (likely due to constipation leading to bacterial translocation through the gut wall) was reported at week 78 (last i.v. golimumab dose received at week 76). The event was considered serious, severe in intensity and probably related to golimumab.

Patients with serious infections, including the death after week 52, were all female and tended to be younger (8.5 *vs* 13.0 years) and weigh less (34.8 *vs* 42.4 kg) than the overall population (Supplementary Table S2, available at *Rheumatology* online). Use of oral glucocorticoids at baseline was lower among patients with serious infections *vs* the overall population (25% *vs* 38%), and

the mean dose in those receiving glucocorticoids was comparable between groups (0.20 *vs* 0.16 mg/kg/day, respectively).

The MedDRA system organ class with the highest incidence of AEs at week 52 was infections and infestations (67%) (Table 3). The most commonly reported AEs were upper respiratory tract infection (21%) and nasopharyngitis (18%). SAEs included disseminated herpes zoster, infective exacerbation of bronchiectasis, sepsis, varicella, mycosis fungoides, suicidal ideation, cellulitis, pneumonia, streptococcal pneumonia and pleural effusion (streptococcal pneumonia and pleural effusion were reported in the same patient). All except varicella, cellulitis and pneumonia resulted in permanent discontinuation of golimumab. New-onset, anterior uveitis in both eyes (considered incipient/very mild and not requiring treatment) was reported in one patient through week 52. The incidences of AEs and SAEs were generally well balanced among ADA- and NAb-positive and ADA- and NAb-negative patients, including the incidence of patients reporting JIA as an AE (data not shown).

Of 115 patients evaluated at week 24, 57 were ANA negative at baseline and 13 (23%) were newly ANA positive at week 24. Of 110 patients evaluated at week 52, 51 were ANA negative at baseline and 13 (25%) were newly ANA positive at week 52. Of these 13 newly positive patients, seven were ANA negative and six were ANA positive at week 24. All six patients ANA positive at week 24 became ANA negative at week 52, and one had discontinued the study. Titres were 1:40 in 11 patients and 1:160 in two patients at week 24, and 1:40 in eight patients, 1:80 in three patients, and 1:160 in two patients at week 52. The assay was kept stable throughout the study. None of the newly positive patients at week 24 and 52 had a history of ANA positivity and none were positive for anti-dsDNA antibodies at baseline, week 28 or week 52.

Discussion

In this open-label phase 3 study in children with pc-JIA, i.v. golimumab plus MTX provided PK exposure similar to that found to be effective in adults with RA [42]. Median trough serum golimumab concentrations and AUCss were generally maintained over time and were similar across age groups and body-weight quartiles, indicating that BSA-based dosing was appropriate to achieve similar PK exposure across the entire pc-JIA age and body-weight range.

i.v. golimumab led to a reduction in clinical signs and symptoms of pc-JIA that was generally maintained through week 52. Overall, consistently high JIA ACR 30, 50, 70 and 90 response rates were observed irrespective of trough serum golimumab concentration quartiles for JIA ACR response, pc-JIA subtypes or prior exposure to biologics that block TNF. Notably, there was a trend towards lower rates of JIA ACR response, including inactive disease, among patients who were biologic non-naïve *vs* biologic naïve. The JIA ACR response rates and the other clinical responses we observed with i.v. golimumab in this study are consistent with those reported for s.c. golimumab and other b-DMARDs in similar phase 3 pc-JIA studies [15, 17, 43–45].

It is well recognized that cross-study comparisons of steady-state trough levels are challenging, particularly when the trough levels are relatively low and, thus, highly variable from study to study. To put the interstudy variability into the context of cross-study comparisons, the steady-state trough concentrations observed in pc-JIA were compared with adult i.v. golimumab pivotal phase 3 rheumatological studies [42, 46, 47]. The median [mean (S.D.)] steady-state trough serum golimumab concentration in pc-JIA patients at week 28 [0.40 (0.50 (0.43)) μg/ml] was within the range of those observed at week 36 in adults with RA, PsA, or AS receiving i.v. golimumab [0.31 (0.41 (0.52)), 0.61 (0.69 (0.58)), and 0.71 (0.74 (0.51)) μg/ml, respectively]. Monoclonal antibodies have been shown to have moderate to high variability [48, 49]. Taking interstudy variability into consideration, these PK data support the conclusion that the steady-state golimumab concentrations observed in children in this study were generally similar to those observed in the adult RA population.

Notably, patients in the highest weight quartile group in this paediatric study had a mean body weight of 73 kg (range: 57.00–142.70 kg), which was similar to the mean body weight of the adult RA population (72 kg; range: 39.00–125.00 kg). In addition, the calculated total dose difference for the 2 mg/kg dose used in the adult RA study *vs* the 80 mg/m^2 dose used in this paediatric study yielded a small dose difference (mean 2%; range: −13% to 16%) for the highest body weight quartile group, demonstrating that the pc-JIA patients in this group received golimumab doses comparable to those in the adult RA population. Therefore, the PK exposure from the highest body weight quartile group provides an internal reference for PK comparison across different age and weight subgroups to demonstrate that PK exposure in all the pc-JIA subgroups was similar to that in the adult RA population.

Median trough golimumab concentration was lower in ADA-positive patients compared with ADA-negative patients and in JIA ACR 30 non-responders compared with responders. The low median golimumab concentration in JIA ACR 30 non-responders overall was because six of 12 JIA ACR 30 non-responders were ADA positive and had median golimumab concentrations below the lower limit of quantification. However, it does not appear that ADA status had an effect on the efficacy profile because six of the 12 non-responders at week 52 were also ADA negative. JIA ACR 30 and 50 response rates were similar in ADA-positive and ADA-negative patients, but higher level responses were less frequent among ADA-positive patients. Baseline characteristics were generally comparable between ADA-positive and ADA-negative patients. There were some differences in select baseline characteristics between NAb-positive and NAb-negative patients; however, these could be due to the

small number of patients in each group and multiple analyses of the data.

The overall safety profile of i.v. golimumab in patients with pc-JIA through week 52 was consistent with that of i.v. golimumab in adult patients with rheumatic disease [42, 46, 47] and s.c. golimumab in patients with pc-JIA [23]. Although there were no deaths through week 52, one death, which was considered to be probably related to i.v. golimumab, was reported at week 78. No deaths have been reported with s.c. golimumab and other b-DMARDs in similar phase 3 pc-JIA studies [15, 17, 43–45]. It is difficult to know if the serious infection rate (6%) is high in this trial because there was no placebo control group. In a recent JIA trial with tocilizumab, the rate of serious infection (4.9/100 patient-years) [14] was comparable to the current trial (6.6/100 patient-years). In earlier JIA trials, one serious infection was reported with etanercept [50] and seven were reported as related to treatment with adalimumab, with others noted but not reported as related to treatment [9]. The manner in which events are reported and the specifics of trial design (e.g. location, population and inclusion/exclusion criteria) have changed over time, possibly influencing infection rates. The number of serious infections in this trial, however, does not seem to be related to steroid use.

The proportion of patients with antibodies to golimumab was relatively higher than that observed in an adult trial in RA (31% *vs* 3%) [51] and correlated with lower median trough golimumab concentration. In addition, 13 patients had newly developed ANAs at week 52, and none of those patients had anti-dsDNA antibodies. A similar phenomenon regarding antibodies and lower trough golimumab concentration and ANA development was previously observed in a trial of infliximab in JIA in which also a higher incidence of SAEs was linked to lower infliximab concentration [7].

It is an ethical requirement of the PRINTO and PRCSG networks that companies involved in trials for registration purposes should continue to provide the drug to children enrolled in a clinical trial until an alternative method of drug provision is identified. As previously reported, this requirement is of particular importance for countries with less resources where children might not have public or private insurance to cover the high cost of b-DMARDs [52]. For this trial, drug provision was stopped after 252 weeks for the children enrolled in the trial who have reached the age of 18 years. i.v. golimumab is currently marketed for RA, PsA or AS in many of the countries (seven out of nine) participating in the trial. The availability of the i.v. formulation might be especially relevant for non-compliant patients during or after adolescence.

A limitation of this study is its open-label, non-randomized, and uncontrolled design that does not allow for a robust evaluation of clinical efficacy. The study was designed this way with the intent to extrapolate the results from efficacy trials in adults.

In conclusion, i.v. golimumab 80 mg/m^2 at weeks 0 and 4 and then q8w through week 52 with weekly MTX was generally well tolerated and provided adequate PK exposure for clinical efficacy in patients with active pc-JIA, including a subset of patients with prior exposure to anti-TNF therapy.

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Data availability statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the trial data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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