Running title: Intravenous golimumab in juvenile idiopathic arthritis

Open-Label Phase 3 Study of Intravenous Golimumab in Patients With Polyarticular Juvenile Idiopathic Arthritis

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**Word Count:** Abstract: 250 words; Text: 4073 words; Tables and Figures: 6; References: 52
ABSTRACT

Objectives

Assess efficacy, pharmacokinetics (PK), and safety of intravenous (IV) golimumab in patients with polyarticular-course juvenile idiopathic arthritis (pc-JIA).

Methods

Children aged 2 to <18 years with active pc-JIA despite methotrexate therapy for ≥2 months received 80 mg/m² golimumab at Weeks 0, 4, then every 8 weeks through Week 52 plus methotrexate 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 American College of Rheumatology (ACR) response and safety were also assessed.

Results

In total, 127 children were treated with IV 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 52. Steady-state trough golimumab concentrations and AUC_{ss} were consistent across age categories and comparable with IV 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 versus antibody-negative patients. Serious infections were reported in 6% of patients, including 1 death due to septic shock.
Conclusion

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

ClinicalTrials.gov number NCT02277444

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

Key Messages

- IV golimumab 80 mg/m² every 8 weeks provided adequate PK exposure in children with pc-JIA.

- IV golimumab generally reduced clinical signs and symptoms in children with pc-JIA through Week 52.

- IV golimumab was generally well tolerated in children with pc-JIA through Week 52.
INTRODUCTION

Juvenile idiopathic arthritis (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 nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular or systemic glucocorticoids as bridge therapy, and synthetic disease-modifying antirheumatic drugs (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 tumour necrosis factor alpha (TNFα). Subcutaneous (SC) and intravenous (IV) golimumab are effective in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) in adults. In a previous study in children with active pc-JIA, SC 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 IV golimumab through 52 weeks of treatment in children with pc-JIA.

PATIENTS AND METHODS

Patients and Study Design

This was a Phase 3, open-label, single-arm, international study conducted in 33 centres in 9 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 enrollment, with a
≥3-month history of pc-JIA and active arthritis (≥5 active joints) despite methotrexate (MTX; ≥10 mg/m²) 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, rheumatoid factor (RF)-positive or RF-negative pc-JIA, systemic JIA with no systemic symptoms for ≥3 months, enthesitis-related arthritis, or polyarticular juvenile psoriatic arthritis.

All eligible patients received 80 mg/m² golimumab IV (maximum single dose of 240 mg, over 30±10 minutes) at Weeks 0 and 4 and then every 8 weeks (q8w) through Week 52 (Supplementary Figure S1). Body surface area (BSA) was calculated at each visit, and the dose was adjusted as needed to maintain 80 mg/m². Commercial MTX was administered weekly at least through Week 28 at the same dosage as at study entry (10 to 30 mg/m² for BSA <1.67 m² or ≥15 mg for BSA ≥1.67 m²) (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 IV 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 IV 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 hours 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 Health Assessment Questionnaire [CHAQ; including parent assessment of overall well-being and pain using VAS (0
to 10 cm]) (29,30), and C-reactive protein [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 titer 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 titer 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\text{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\text{ss} at Week 52.

Efficacy endpoints included the JIA American College of Rheumatology (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 IV 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 minutes); 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 to 10.5 for moderate disease activity [MDA], 1.1 to 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 nonlinear 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 IV 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 [NRI] for completely missing data and last observation carried forward [LOCF] 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 IV golimumab, and were included in the full analysis data set (Figure 1). Of these 127 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).

Efficacy

As shown in Table 2, improvement from baseline in the JIA ACR component scores was observed as early as 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 (Figure 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 (Figure 2B). Clinical remission while on medication was achieved by 2% of patients at Week 28 and 13% at Week 52 (Figure 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 (Figure 2C). The pattern of improvement was similar for parent assessment of patient pain (Figure 2C). A decrease in mean JADAS 71 score was observed as early as Week 4 and continued through Week 52 (Figure 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 psoriatic arthritis (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 versus 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 IV golimumab was similar to that in the adult RA population (Figure 3A and 3B). The overall median steady-state trough golimumab concentration in pc-JIA patients was 0.40 (mean±standard deviation [SD]: 0.50±0.43) µg/mL at Week 28 and 0.45 (mean±SD: 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±SD 0.41±0.52] µg/mL) in the adult RA population (Figure 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\textsubscript{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 (Figure 3B). The AUC\textsubscript{ss} values in pc-JIA patients were slightly higher than the AUC\textsubscript{ss} (248 µg·day/mL) observed in the adult RA population (Figure 3B).

Through Week 52, 39 of 125 (31%) patients with appropriate samples were ADA positive and 24 (19%) were positive for golimumab neutralizing antibodies (NAbs). Peak titer for antibodies to golimumab was <10 in 5 patients, ≥10 to <100 in 17 patients, ≥100 to <1000 in 13 patients, and ≥1000 in 4 patients. Select baseline demographic and disease characteristics
were generally comparable between ADA- or NAb-positive and ADA- or NAb-negative patients (Supplementary Table S1). NAb-positive patients had a slightly lower baseline weight than the other patient categories (36.9 kg versus 42.2 to 44.0 kg). In addition, a greater proportion of ADA- and NAb-positive versus ADA- and NAb-negative patients were diagnosed with oligoarticular extended pc-JIA (10.3% and 12.5% versus 4.7% and 6.7%, respectively), and a greater proportion of NAb-positive patients were diagnosed with polyarticular rheumatoid factor-negative pc-JIA versus the other patient categories (41.7% versus 26.7% to 35.9%). Median trough golimumab concentration tended to be lower in ADA-positive patients than in ADA-negative patients (0.00 [n=32] versus 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) versus 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 1 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 1 patient, was considered to be nonserious and not
related to golimumab. No deaths were reported through Week 52, but 1 death due to septic shock (likely due to constipation leading to bacterial translocation through the gut wall) was reported at Week 78 (last IV 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 versus 13.0 years) and weigh less (34.8 versus 42.4 kg) than the overall population (Supplementary Table S2). Use of oral glucocorticoids at baseline was lower among patients with serious infections versus the overall population (25% versus 38%), and the mean dose in those receiving glucocorticoids was comparable between groups (0.20 versus 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 (21.3%) 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 plural 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 1 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, 7 were ANA negative and 6 were ANA positive at Week 24. All 6 patients ANA positive at Week 24 became ANA negative at Week 52, and 1 had discontinued the study. Titers were 1:40 in 11 patients and 1:160 in 2 patients at Week 24, and 1:40 in 8 patients, 1:80 in 3 patients, and 1:160 in 2 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, IV 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.

IV 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 toward lower rates of JIA ACR response, including inactive disease, among patients who were biologic non-naïve versus biologic naïve. The JIA ACR response rates and the other clinical responses we observed with IV golimumab in this study are consistent with those reported for SC 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 IV golimumab pivotal Phase 3 rheumatologic studies (42,46,47). The median (mean±SD) 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 IV 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 to 142.70 kg), which was similar to the mean body weight of the adult RA population (72 kg; range: 39.00 to 125.00 kg). In addition, the calculated total dose difference for the 2 mg/kg dose used in the adult RA study versus 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 6 of 12 JIA ACR 30 non-responders were ADA positive and had median golimumab concentrations below the lower limit of quantitation. However, it does not appear that ADA status had an effect on the efficacy profile because 6 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 IV golimumab in patients with pc-JIA through Week 52 was consistent with that of IV golimumab in adult patients with rheumatic disease (42,46,47) and SC golimumab in patients with pc-JIA (23). Although there were no deaths through Week 52, 1 death, which was considered to be probably related to IV golimumab, was reported at Week 78. No deaths have been reported with SC 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, 1 serious infection was reported with etanercept (50) and 7 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 (eg, 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% versus 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 where 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. IV golimumab is currently marketed for RA, PsA, or AS in many of the countries (7 out of 9) participating in the trial. The availability of the IV formulation might be especially relevant for non-compliant patients during or after adolescence.

A limitation of this study is its open-label, nonrandomized, 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, IV golimumab 80 mg/m² 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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FUNDING

This work was supported by Janssen Research & Development, LLC, which provided financial support for this work and had a role in the study design; collection, analysis, and interpretation of data; writing of the report; and the decision to submit the article for publication.

ACKNOWLEDGMENTS

We thank all PRINTO and PRCSG centres and all families who contributed to the study. We also thank Dr. Lyudmila Grebenkina of Togliatti City Clinical Hospital No. 5, Pediatric Department, Togliatti, Russian Federation for her contributions to the study. Writing and editorial assistance were provided by Holly Capasso-Harris, PhD, of Synchrogenix, a Certara Company, Wilmington, DE and funded by Janssen Research & Development, LLC. Programming was performed by Renping Zhang of Janssen Research & Development, LLC.

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ADDITIONAL INFORMATION

Coauthor Vladimir Keltsev, MD, passed away in January 2020.

CONFLICTS OF INTEREST

Dr. Ruperto has served as a paid consultant for or received speaker fees or honoraria (<$10,000 each) from AbbVie, Ablynx, AstraZeneca-MedImmune, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EMD Serono, GSK, Hoffmann-La Roche, Janssen, Merck, Novartis, Pfizer, R-Pharma, Sanofi, Servier, Sinergie, Sobi, and Takeda and is employed full time at the IRCCS Istituto Giannina Gaslini, which has received contributions (>-$10,000 each, reinvested for research activities of the hospital in a fully independent manner, without any commitment with third parties) from the following in the last 3 years: Bristol-Myers Squibb, Eli Lilly, GSK, Hoffmann-La Roche, Janssen, Novartis, Pfizer, and Sobi. Dr. Brunner has served as a paid consultant for or received speaker fees or honoraria (>-$10,000 each) from Novartis and Roche.
Dr. Schmeling has received funding for industry-driven clinical trials/registries from Bristol-Myers Squibb, Janssen, Pfizer, Roche, and USB. Dr. Xavier has served as a paid consultant for or received speaker fees or honoraria (<$10,000 each) from AbbVie, Eli Lilly, Novartis, Pfizer, and Roche. Dr. Clark, Ms. Bensley, Dr. Li, Dr. Lo, Dr. Leu, Dr. Hsu, Dr. Hsia, and Dr. Xu are employees of Janssen Research & Development, LLC, a wholly owned subsidiary of Johnson & Johnson, and own stock or options in Johnson & Johnson. Dr. Martini has served as a paid consultant for or received speaker fees or honoraria (<$10,000 each) from Eli Lilly, EMD Serono, Janssen, Novartis, Pfizer, and AbbVie. Dr. Lovell has served as a paid consultant for or received speaker fees or honoraria (<$10,000 each) from Abbott, AbbVie, Amgen, AstraZeneca Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Forest Research, GSK, Hoffmann-La Roche, Janssen, Novartis, Pfizer, Takeda, UBC, and Wyeth Pharmaceuticals. Dr. Pacheco-Tena, Dr. Louw, Dr. Vega-Cornejo, Dr. Spindler, Dr. Kingsbury, Dr. Borzutzky, Dr. Cuttica, Dr. Inman, Dr. Malievskiy, Dr. Scott, Dr. Keltsev, Dr. Terreri, Dr. Viola, Dr. Pedrosa Fernandes, Dr. Maldonado Velázquez, and Dr. Henrickson have nothing to declare.

AUTHOR CONTRIBUTIONS

All authors had full access to study data, reviewed and revised the manuscript, and all who were able approved the final version to be published. All authors were involved in the decision to submit the manuscript for publication and had the right to accept or reject comments or suggestions. All authors attest to the completeness and veracity of data and data analyses. Consistency in reporting the study data to healthcare authorities and institutional review boards was ensured by Janssen Research & Development, LLC. The study was designed jointly by academic authors (N. Ruperto, H.I. Brunner, A. Martini, D.J. Lovell) and Janssen Research & Development, LLC, authors (M. Clark, K. Bensley, X. Li, K.H. Lo, J.H. Leu, C.-H. Hsu, E. Hsia,
Z. Xu), with data collected by PRINTO/PRCSG centres. The first and subsequent versions of the manuscript were written by N. Ruperto and H.I. Brunner, edited by A. Martini and D.J. Lovell, and revised critically by all remaining co-authors.

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DATA SHARING 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.
FIGURE LEGENDS

Figure 1. Patient disposition

*Adds up to 51 because 1 patient had more than 1 reason for ineligibility

AE, adverse event; JIA, juvenile idiopathic arthritis; n, number of patients

Figure 2A-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 = 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 (SD) CHAQ and parent assessment of pain scores. (D) Mean (95% CI) JADAS 71 scores. 95% CI is based on normal approximation: mean ± 1.96 × SD/√N. C and D are based on observed data.

ACR, American College of Rheumatology; BSL, baseline; CHAQ, Childhood Health Assessment Questionnaire; CI, confidence interval; HDA, high disease activity; ID, inactive disease; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; LDA, low disease activity; LOCF, last observation carried forward; N, all treated patients; n, number of evaluable patients; NRI, non-responder imputation; SD, standard deviation

Figure 3A-B. 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 1st quartile, and the upper edges of the boxes represent the 3rd quartile. Whiskers represent the most extreme observations within the 1.5× interquartile range.

AUC<sub>ss</sub>, steady-state area under the curve; JIA, juvenile idiopathic arthritis; n, number of patients in the population; RA, rheumatoid arthritis; WK, week
Table 1. Baseline demographics, disease characteristics, and prior arthritis treatment

| Characteristic | Golimumab (N=127) |
|----------------|--------------------|
| Age, 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, kg     | 42.4 (29.2, 57.0)  |
| BSA, m²        | 1.3 (1.0, 1.6)     |
| Duration of disease, years | 1.4 (0.5, 4.0) |
| History of uveitis, n (%) | 3 (2.4) |
| ILAR classification, n (%) | |
| Polyarticular rheumatoid factor-negative | 54 (42.5) |
| Polyarticular rheumatoid factor-positive  | 44 (34.6) |
| Enthesitis-related arthritis              | 12 (9.4) |
| Oligoarticular extended                   | 8 (6.3) |
| Juvenile psoriatic arthritis              | 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) |
| Characteristic                                      | Golimumab (N=127) |
|----------------------------------------------------|-------------------|
| Other\(^a\)                                        | 10 (38.5)         |

Baseline JIA medications\(^b\)

- Methotrexate, n (%)                                  | 127 (100)         |
- Mean (SD) methotrexate dose, mg/m\(^2\)/wk            | 13.6 (4.5)        |
- s-DMARDs other than methotrexate, n (%)              | 13 (10.2)         |
- Oral glucocorticoids, n (%)                          | 47 (37.0)         |
- Mean (SD) prednisone or equivalent dose, mg/kg/day   | 0.16 (0.1)        |
- NSAIDs, n (%)                                       | 92 (72.4)         |

Prior JIA medications\(^c\), n (%)

- Methotrexate                                       | 127 (100)         |
- s-DMARDs other than methotrexate\(^d\)              | 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)        |

Values are median (IQ range) unless otherwise noted.

\(^a\)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 cyclosporine (n=2) and azathioprine (n=1)
ANA, antinuclear antibody; b-DMARD, biologic disease-modifying antirheumatic drug;
BSA, body surface area; DMARD, disease-modifying antirheumatic drug; ILAR, International
League of Associations for Rheumatology; IQ, interquartile; JIA, juvenile idiopathic arthritis; N,
all treated patients; n, number of patients; NSAID, nonsteroidal anti-inflammatory drug; SD,
standard deviation; s-DMARD, synthetic disease-modifying antirheumatic drug; TNF, tumour
necrosis factor
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                   |               |                |                |                |
| MD global of disease activity, 0-10 cm  | 5.5 (4.5, 6.8) | 2.2 (1.0, 3.8) | 0.5 (0.1, 1.2) | 0.3 (0.0, 1.4) |
| VAS                                     |               |                |                |                |
| 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/dLb                             | 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, minutes | 40 (20, 60)    | 5 (0, 30)      | 0 (0, 15)      | 0 (0, 15)      |
| JADAS 71, mean (95% confidence interval) | 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) |
| Characteristic                  | Baseline   | Week 4    | Week 28   | Week 52   |
|--------------------------------|------------|-----------|-----------|-----------|
| 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) |

All values are median (IQ range) unless otherwise noted.

\( ^a \)n=122

\( ^b \)Normal is ≤0.287 mg/dL

95% confidence interval is based on normal approximation: mean ± 1.96 × SD/\(\sqrt{N}\)

CHAQ, Childhood Health Assessment Questionnaire; CRP, C-reactive protein; IQ, interquartile; JADAS 71, Juvenile Arthritis Disease Activity Score 71 joints evaluated; JIA, juvenile idiopathic arthritis; MD, medical doctor; VAS, visual analogue scale
Table 3. Summary of adverse events through Week 52

| Event                                                                 | 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                  | 11 (8.7)           |
| Patients with ≥1 AE                                                 | 108 (85.0)         |
| Patients with ≥1 severe AE                                          | 5 (3.9)            |
| Patients with ≥1 SAE                                                | 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                                          | 83 (65.4)          |
| ≥1 serious infection                                                | 7 (5.5)            |
| ≥1 opportunistic infection                                          | 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                          | 3 (2.4)            |
| Patients with ≥1 malignancy\(^b\)                                   | 1 (0.8)            |
| Patients with active tuberculosis                                   | 0                  |
| Positivity for ANA/anti-dsDNA antibodies\(^c\)                      | 13 (25.5)          |
| Common AEs (occurring in ≥5% of patients) by SOC and related        |                    |
| Preferred Terms                                                     |                    |
| Infections and infestations                                         | 85 (66.9)          |
| Medical Condition                                      | Golimumab (N=127) |
|-------------------------------------------------------|--------------------|
| 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)          |
| Juvenile idiopathic arthritis                         | 14 (11.0)          |
| Nervous system disorders                               | 20 (15.7)          |
| Headache                                              | 14 (11.0)          |
| Investigations                                        | 13 (10.2)          |
| Alanine aminotransferase increased                    | 7 (5.5)            |

All values are n (%) unless otherwise noted.

*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; CI, confidence interval; N, all treated patients; n, number of patients; SAE, serious adverse event; SOC, system organ class
Figure 1. Patient disposition

*Adds up to 51 because 1 patient had more than 1 reason for ineligibility
AE, adverse event; JIA, juvenile idiopathic arthritis; n, number of patients
Figure 2A-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 = inactive disease at each visit for ≥6 months while on medication for poly-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 (SD) CHAQ and parent assessment of pain scores. (D) Mean (95% CI) JADAS 71 scores. 95% CI is based on normal approximation: mean ±1.96×SD/√N. C and D are based on observed data.

ACR, American College of Rheumatology; BSL, baseline; CHAQ, Childhood Health Assessment Questionnaire; CI, confidence interval; HDA, high disease activity; ID, inactive disease; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; LDA, low disease activity; LOCF, last observation carried forward; N, all treated patients; n, number of evaluable patients; NRI, non-responder imputation; SD, standard deviation.
Figure 3A-B. Observed steady-state serum trough golimumab concentrations (A) and model-predicted AUCss (B) at Week 28

The horizontal lines within the boxes represent the medians, the lower edges of the boxes represent the 1st quartile, and the upper edges of the boxes represent the 3rd quartile. Whiskers represent the most extreme observations within the 1.5× interquartile range.

AUCss, steady-state area under the curve; JIA, juvenile idiopathic arthritis; n, number of patients in the population; RA, rheumatoid arthritis; WK, week