The Journal of Rheumatology 2025;xx:xxxx
doi:10.3899/jrheum.2024-0536
First Release July 1 2025

The Journal of Rheumatology

Clinically Inactive Disease and Remission in Patients With Juvenile Idiopathic Arthritis Receiving Tofacitinib: Post Hoc Analysis of a Phase III Trial

Alessandro Consolaro[1], Nicolino Ruperto[2], Daniel J. Lovell[3], Olga Synoverska[4], Carlos Abud-Mendoza[5], Alberto Spindler[6], Yulia Vyzhga[7], Ekaterina Alexeeva[8], Jeffrey Chaitow[9], Peter Chiraseveenuprapund[10], Irina Lazariciu[11], Lori Stockert[12], Mary Jane Cadatal[13], Annette Diehl[12], and Hermine I. Brunner[3], on behalf of the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG)

ABSTRACT. ***Objective.*** To evaluate rates of clinically inactive disease (CID) and remission in patients with juvenile idiopathic arthritis (JIA) receiving tofacitinib using the 2021 Juvenile Arthritis Disease Activity Score (JADAS) thresholds and American College of Rheumatology (ACR) criteria.

Methods. This post hoc analysis included patients with active JIA (polyarticular-course JIA, psoriatic arthritis, or enthesitis-related arthritis) enrolled in a phase III randomized withdrawal study of tofacitinib. In part 1 (weeks 0-18), patients received open-label tofacitinib. In part 2 (weeks 18-44), patients who achieved ACR improvement ≥ 30% were randomized to tofacitinib or placebo for 26 weeks or until JIA flare. Disease activity was assessed using the JADAS in 10 joints (JADAS10) based on C-reactive protein, with interpretation according to 2021 polyarthritis thresholds. JADAS10 remission was defined as ≥ 24 continuous weeks of JADAS10 CID (JADAS10-CID). ACR CID (ACR-CID) and ACR clinical remission were also assessed.

Results. Of 225 patients with JIA in part 1, 173 (76.9%) were randomized in part 2 to continue tofacitinib or switch to placebo. Rates of JADAS10-CID and ACR-CID increased throughout part 1 to 30.5% and 15.8% (week 18), respectively. In part 2, these were sustained with tofacitinib (week 44: 35.2% [JADAS10-CID], 25% [ACR-CID]) and decreased when patients switched to placebo (week 44: 25.9% [JADAS10-CID], 15.3% [ACR-CID]). A small proportion of patients achieved JADAS10 remission at week 44 (tofacitinib: 14.8%; placebo: 7.1%).

Conclusion. In patients with JIA receiving tofacitinib, JADAS10-CID and ACR-CID rates improved rapidly and were sustained over time, and a small proportion of patients achieved JADAS10 remission. Inactive disease is a feasible treatment target in patients receiving tofacitinib. (ClinicalTrials.gov: NCT02592434)

Key Indexing Terms: arthritis, biological therapy, disease activity score, juvenile idiopathic arthritis, outcomes, pediatric rheumatic diseases

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and is associated with pain and poor physical functioning, which contribute to impairment in health-related quality of life (HRQOL).[1-3] Disease activity is associated with worse HRQOL in children with JIA,[4,5] and studies have shown that patient outcomes are improved if low levels of disease activity are achieved.[3,6] Thus, clinically inactive disease (CID) and clinical remission are important

[1]A. Consolaro, MD, PhD, IRCCS Istituto Giannina Gaslini, and Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Mother-Child Health (DINOGMI), University of Genova, Genova, Italy; [2]N. Ruperto, MD, MPH, Università degli Studi di Milano-Bicocca, Milan, and Fondazione IRCCS San Gerardo dei Tintori, Reumatologia Pediatrica/PRINTO, Monza, Italy; [3]D.J. Lovell, MD, MPH, H.I. Brunner, MD, MSc, MBA, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [4]O. Synoverska, MD, Regional Children's Hospital, Ivano-Frankivsk, Ukraine; [5]C. Abud-Mendoza, MD, Regional Unit of Rheumatology and Osteoporosis at Central Hospital, Faculty of Medicine, San Luis Potosí, Mexico; [6]A. Spindler, MD, Centro Médico Privado de Reumatologia, Tucumán, Argentina; [7]Y. Vyzhga, MD, PhD, Vinnytsya National Medical University N Pirogov, Vinnytsya, Ukraine; [8]E. Alexeeva, MD, PhD, National Medical Research Center for Children's Health Federal State Autonomous Institution of the Russian Federation Ministry of Health, and I.M. Sechenov First Moscow State Medical University (Sechenovskiy University), Moscow, Russia; [9]J. Chaitow, MBBCh, FRACP, The Children's Hospital Westmead, Sydney, New South Wales, Australia; [10]P. Chiraseveenuprapund, MD, Rady Children's Hospital, San Diego, California, USA; [11]I. Lazariciu, PhD, Pfizer Inc., New York, New York, USA; [12]L. Stockert, MS, A. Diehl, MPH, MBA, Pfizer Inc., Collegeville, Pennsylvania, USA; [13]M.J. Cadatal, MSc, Pfizer Inc., Manila, Philippines.

Address correspondence to Prof. A. Consolaro, Università di Genova, Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, 16147, Genova, Italy. Email: alessandroconsolaro@gaslini.org.

Accepted for publication April 16, 2025.

treatment targets in JIA, as is minimal disease activity in select cases.[7]

Several tools for the assessment of improvements in JIA disease activity have been developed for use in randomized clinical trials and routine clinical practice, such as the Juvenile Arthritis Disease Activity Score in 10 joints (JADAS10)[8,9] and the American College of Rheumatology (ACR) response criteria for CID and remission thresholds.[10,11] New JADAS10 thresholds to separate the states of CID (JADAS10-CID), minimal disease activity (JADAS10-MiDA), moderate disease activity (JADAS10-MoDA), and high disease activity (JADAS10-HDA) for nonsystemic forms of JIA were developed and validated in 2021 and endorsed by the ACR.[12] Thresholds were defined using a large multinational data set of nearly 2000 patients across 35 pediatric rheumatology centers in 49 countries in a study coordinated by the Paediatric Rheumatology International Trials Organisation (PRINTO).[12] These thresholds incorporated objective data for disease activity as well as subjective ratings of disease activity by pediatric rheumatologists and were validated using 4 different samples that included nearly 5000 patients with JIA.[12] Using the 2021 thresholds, JADAS10-CID is defined as a JADAS10 score of ≤ 2.7 in patients with polyarthritis and ≤ 1.4 for those with oligoarthritis—a slightly less stringent threshold compared to the 2012-2014 JADAS10 threshold score of ≤ 1 for both subtypes.[12]

Tofacitinib is an oral Janus kinase inhibitor for patients with JIA. The pharmacokinetic profile and dosing of tofacitinib in patients with polyarticular-course JIA have been demonstrated in a phase I study,[13] and efficacy and safety have been demonstrated in a double-blind placebo-controlled phase III withdrawal trial.[14]

This post hoc analysis used data from the phase III trial to evaluate disease control in patients with JIA treated with tofacitinib, measured by the achievement of CID or clinical remission according to the 2021 JADAS10 thresholds, as well as by the ACR criteria.

METHODS

Study design and patients. This analysis used data from all patients enrolled in the phase III, 2-part, randomized, double-blind, placebo-controlled withdrawal study (ClinicalTrials.gov: NCT02592434) conducted at PRINTO and Pediatric Rheumatology Collaborative Study Group (PRCSG)[15] centers; full study details have been reported previously.[14] Briefly, eligible patients were aged 2 to < 18 years and met the International League of Associations for Rheumatology (ILAR) classification criteria[16] for 1 of the following JIA categories: extended oligoarthritis, rheumatoid factor (RF)-positive or RF-negative polyarthritis, systemic JIA (sJIA) without systemic features for 6 months prior to enrollment, psoriatic arthritis (PsA), or enthesitis-related arthritis (ERA). Patients with polyarticular-course JIA (extended oligoarthritis, RF-positive or RF-negative polyarthritis, or sJIA without systemic features) were required to have ≥ 5 active joints at enrollment. Those with PsA or ERA were required to have ≥ 3 active joints at enrollment. Stable doses of nonsteroidal antiinflammatory drugs, methotrexate (≤ 25 mg/week or ≤ 20 mg/m^2/week, whichever was lower), and oral glucocorticoids (GCs; ≤ 0.2 mg/kg/day of prednisone equivalent or ≤ 10 mg/day, whichever was lower) could be continued throughout parts 1 and 2 of the trial in patients receiving tofacitinib or placebo.

In part 1 (open-label, run-in phase; weeks 0-18), patients received tofacitinib 5 mg tablets twice daily or a bodyweight-based lower equivalent dose of an oral solution (1 mg/mL) until week 18 or JIA flare. In part 2 (double-blind phase; weeks 18-44), patients achieving ACR ≥ 30% response[17] at week 18 of part 1 were randomized 1:1 to continue receiving tofacitinib or switch to placebo for 26 weeks or until JIA flare. Patients who experienced a JIA flare at any time during the study (part 1 or part 2) were discontinued from the study. JIA flare was defined as a worsening of ≥ 30% in ≥ 3 of 6 ACR core set variables, with ≤ 1 of the variables improving by ≥ 30%, in line with PRCSG and PRINTO flare criteria.[18]

Post hoc analyses assessing disease activity and physical function. Disease activity was assessed using JADAS10 (scored 0-40) based on C-reactive protein (CRP; JADAS10-CRP; referred to herein as JADAS10).[19] JADAS10-HDA, JADAS10-MoDA, JADAS10-MiDA, and JADAS10-CID were defined based on the 2021 thresholds as JADAS10 scores of > 17, 6.1-17, 2.8-6, and ≤ 2.7, respectively, for patients with polyarthritis (> 4 active joints), and > 13, 4.1-13, 1.5-4, and ≤ 1.4, respectively, for patients with oligoarthritis (≤ 4 active joints).[12] JADAS10 remission was defined as ≥ 24 continuous weeks of JADAS10-CID, analogous to the ACR definition of clinical remission (≥ 24 continuous weeks of CID in accordance with ACR criteria [ACR-CID]).[10,11] Given the study design, JIA remission could only be achieved in part 2 since the duration of part 1 was 18 weeks. ACR-CID was assessed (ie, no joints with active arthritis; no fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA; no active uveitis; normal erythrocyte sedimentation rate or CRP level within normal limits in the laboratory [where tested] or, if elevated, not attributable to JIA; best possible physician global assessment of disease activity score on the scale used; and duration of morning stiffness ≤ 15 minutes)[10] throughout part 1 and part 2. ACR clinical remission (ACR-CID for ≥ 24 continuous weeks) was also assessed. Moreover, JADAS10-CID or remission plus normal physical function and ACR-CID plus normal physical function were evaluated. Normal physical function was defined as a Childhood Health Assessment Questionnaire–Disability Index (CHAQ-DI) score of 0, based on the cross-culturally adapted CHAQ-DI.[20]

Statistical analysis. JADAS10 was analyzed first as a continuous variable and then as binary variables (ie, JADAS10-CID or remission: yes/no). ACR-CID and outcomes combined with normal physical function (CHAQ-DI score of 0; yes/no) were analyzed as binary variables. For all binary endpoints, any missing values prior to discontinuation during part 1 or part 2 were imputed using last observation carried forward. Patients who discontinued from part 2 for any reason were considered as having active disease from the date of their double-blind treatment discontinuation visit through week 44, except patients who met ACR-CID criteria at the time of discontinuation. Likewise,

patients who discontinued were considered not to have achieved normal function, as measured by CHAQ-DI, after the date of discontinuation. In addition to the binary classification, patients were categorized as having JADAS10-HDA, JADAS10-MoDA, JADAS10-MiDA, or JADAS10-CID, with no imputation for missing data. JADAS10 scores were rounded to 1 decimal place prior to classifying patients into disease activity states.

Summary statistics were provided for the continuous data for part 1 and by treatment (tofacitinib or placebo) for part 2. Given that these analyses were post hoc, the reported *P* values (95% CI) are nominal.

All efficacy endpoints reported here were calculated by Pfizer from Case Report Form data, with the exception of ACR-CID status and JIA flare (defined according to PRCSG and PRINTO criteria),[18] which were assessed and confirmed in real time, according to validated criteria, by independent evaluators at the PRINTO/PRCSG centralized coordinating centers.[10,14,17]

RESULTS

Patients. A total of 225 patients with JIA entered part 1 and 173 patients (76.9%) were randomized in part 2 to either continue receiving tofacitinib (N = 88) or to switch to placebo (N = 85). Details of patient demographics, baseline characteristics, and disposition throughout the trial have been reported previously.[14] Briefly, patients were mostly female and White, 184/225 patients (81.8%) had polyarticular-course JIA, 20/225 (8.9%) had PsA, and 21/225 (9.3%) had ERA. Median age at baseline was 13 years (IQR 9-15), median age at diagnosis was 8 years (IQR 4-12.3), and median disease duration was 2.5 years (IQR 1-5.6). Overall, 65.3% (147/225) of patients were receiving concomitant methotrexate and 32.4% (73/225) were receiving a low dose of oral GCs. The proportion of patients who discontinued treatment in part 2 was higher in the placebo vs tofacitinib group (55.3% [47/85] vs 30.7% [27/88], respectively). The most common reason for discontinuation was insufficient clinical response, reported in 51.8% [44/85] and 25% [22/88] of patients receiving placebo or tofacitinib, respectively.

At part 1 baseline, patients had active disease, as indicated by a mean disease activity score of 19.6 (SD 5.6; representing JADAS10-HDA [defined as a score of > 17]). An early and rapid decrease in mean JADAS10 was observed with tofacitinib during part 1 of the study; by week 18, the mean score was 6.1 (SD 4.7), corresponding with JADAS10-MoDA (defined as a score of 6.1-17), although just above the upper limit of JADAS10-MiDA (defined as a score of 2.8-6), per the 2021 thresholds for patients with polyarthritis (Figure 1A).[12] At the start of part 2 (week 18; following randomization of patients achieving ACR ≥ 30% improvement), the mean JADAS10 score was 5.7 (SD 4.2; JADAS10-MiDA) in patients randomized to tofacitinib and 5.4 (SD 4.4; JADAS10-MiDA) in patients randomized to placebo. For patients who completed part 2 of the study, mean disease activity remained in the minimal range at week 44, with mean JADAS10 of 3.9 (SD 3.7) and 3.5 (SD 3.2) for tofacitinib and placebo, respectively (Figure 1B; observed-case analyses). At the start of part 1, the majority of patients had JADAS10-HDA (Figure 2). At the start of part 2, following 18 weeks of open-label treatment with tofacitinib (week 18; postrandomization), only 1 patient randomized to placebo and no patients randomized to tofacitinib had JADAS10-HDA; all other patients had achieved JADAS10-MoDA, JADAS10-MiDA, or JADAS10-CID activity, which were each evenly distributed across treatment groups. By week 44, approximately half of the patients remaining in the study had achieved JADAS10-CID (Figure 2; observed-case analysis).

Achievement of JADAS10-CID and remission. The proportion of patients receiving tofacitinib who achieved JADAS10-CID gradually increased throughout part 1 of the study; by the end of part 1 (week 18), JADAS10-CID was achieved by 30.5% (58/190) of patients (Figure 3A). Of those who entered part 2 (week 18), 30.7% (27/88) and 36.5% (31/85) of patients randomized to the tofacitinib or placebo group, respectively, had achieved JADAS10-CID (Figure 3B). The proportion of patients who achieved JADAS10-CID was generally consistent over time throughout part 2 in the tofacitinib group. However, in the placebo group, the proportion of patients achieving JADAS10-CID declined from week 18 to week 20 and subsequently remained stable up to week 44. By week 44, 35.2% (31/88) and 25.9% (22/85) of randomized patients receiving tofacitinib or placebo, respectively, had achieved JADAS10-CID. From week 20 onward, rates of JADAS10-CID were numerically higher in tofacitinib-treated patients vs patients who received placebo (Figure 3B). Figure 3B also shows the rates of JADAS10 remission at each time point throughout part 2, as of week 24. Rates of remission increased over time and were numerically higher in patients receiving tofacitinib vs placebo (14.8% [13/88] vs 7.1% [6/85] of randomized patients at week 44).

Normal physical function (based on a CHAQ-DI score of 0)[20] was assessed in combination with JADAS10-CID and JADAS10 remission. Rates of JADAS10-CID plus normal physical function increased throughout part 1 up to 17.9% (34/190) at week 18 in patients receiving open-label tofacitinib. In the tofacitinib group, the rate of JADAS10-CID plus normal physical function increased throughout part 2, from 15.9% (14/88; part 2 baseline) up to 27.3% (24/88; week 44; Supplementary Figure S1, available with the online version of this article). Rates of JADAS10 remission plus normal physical function increased in part 2 from week 28 onward and were numerically higher in patients receiving tofacitinib vs placebo (14.8% [13/88] vs 5.9% [5/85] of randomized patients at week 44; Supplementary Figure S1).

Achievement of ACR-CID and clinical remission. In part 1, the proportion of tofacitinib-treated patients achieving ACR-CID steadily increased up to 15.8% (30/190) at week 18 (Figure 4A). Of those who entered part 2 (week 18), ACR-CID was achieved at part 2 baseline by 10.2% (9/88) of patients randomized to tofacitinib and 24.7% (21/85) of patients randomized to placebo (Figure 4B). In part 2, the proportion of patients achieving ACR-CID increased over time in patients receiving tofacitinib (up to 25% [22/88] at week 44). In the placebo group, the proportion of patients achieving ACR-CID decreased from week 18 to week 20 and then remained stable up to week 44 (15.3% [13/85]). Rates of ACR-CID were similar in patients receiving tofacitinib or placebo from weeks 20-28.

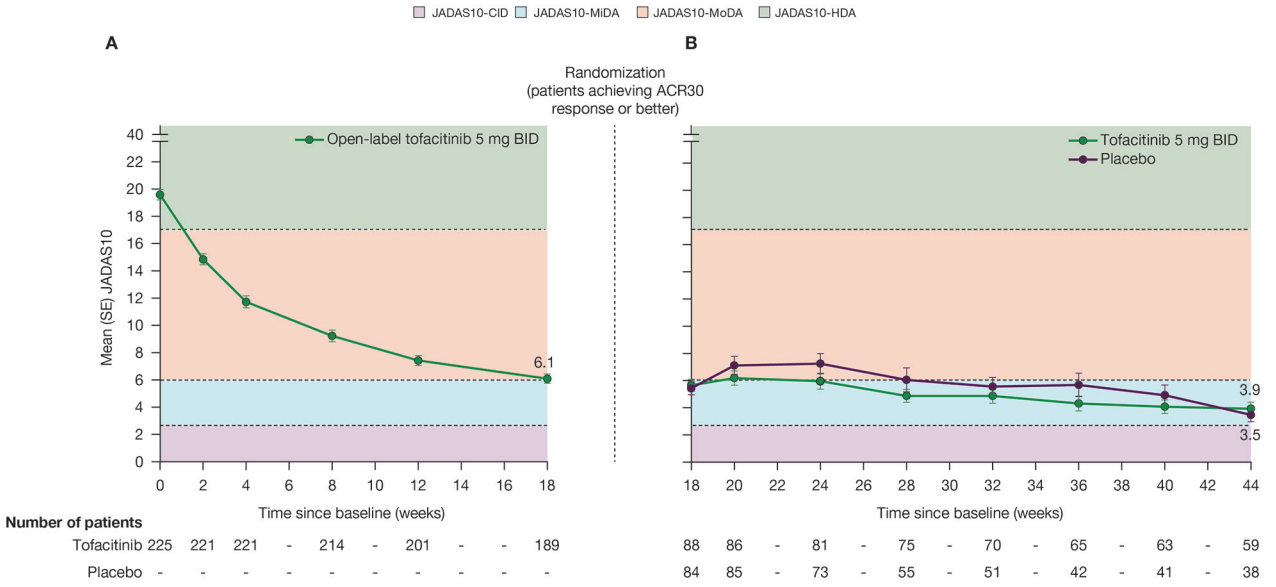

Figure 1. Mean JADAS10 during (A) part 1 (all enrolled patients) and (B) part 2 (patients randomized to either tofacitinib[a] or placebo). Shading represents the 2021 score thresholds for the states of JADAS10-CID (≤ 2.7), JADAS10-MiDA (2.8-6), JADAS10-MoDA (6.1-17), and JADAS10-HDA (> 17) in patients with polyarthritis.[12] The number of patients represents the number of evaluable patients at each visit. Data are shown as observed with no imputation for missing scores. [a] Tofacitinib 5 mg BID or equivalent weight-based lower dose in patients < 40 kg. ACR30: American College of Rheumatology improvement by ≥ 30%; BID: twice daily; CID: clinically inactive disease; HDA: high disease activity; JADAS10: Juvenile Arthritis Disease Activity Score in 10 joints, based on C-reactive protein; MiDA: minimal disease activity; MoDA: moderate disease activity; SE: standard error.

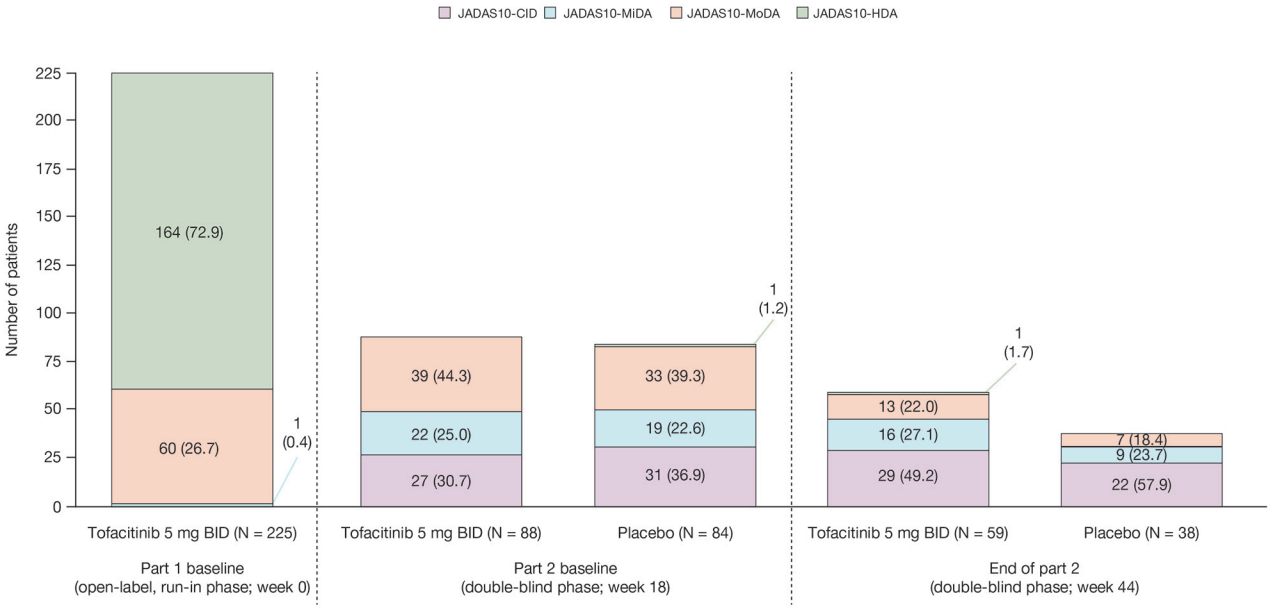

Figure 2. Patients with JADAS10-CID, JADAS10-MiDA, JADAS10-MoDA, and JADAS10-HDA[a] at part 1 baseline (all enrolled patients), part 2 baseline (patients randomized to either tofacitinib[b] or placebo), and week 44. Data are presented as n (%). N represents the number of evaluable patients. Data are shown as observed with no imputation for missing scores. Stable doses of nonsteroidal antiinflammatory drugs, methotrexate, and oral glucocorticoids could be continued throughout part 1 and part 2 of the trial in patients receiving tofacitinib or placebo. [a] JADAS10-CID, JADAS10-MiDA, JADAS10-MoDA, and JADAS10-HDA were defined as JADAS10 score of ≤ 2.7, 2.8-6, 6.1-17, and > 17, respectively, for patients with polyarthritis, and ≤ 1.4, 1.5-4, 4.1-13, and > 13, respectively, for patients with oligoarthritis.[12] [b] Tofacitinib 5 mg BID or equivalent weight-based lower dose in patients < 40 kg. BID: twice daily; CID: clinically inactive disease; HDA: high disease activity; JADAS10: Juvenile Arthritis Disease Activity Score in 10 joints, based on C-reactive protein; MiDA: minimal disease activity; MoDA: moderate disease activity.

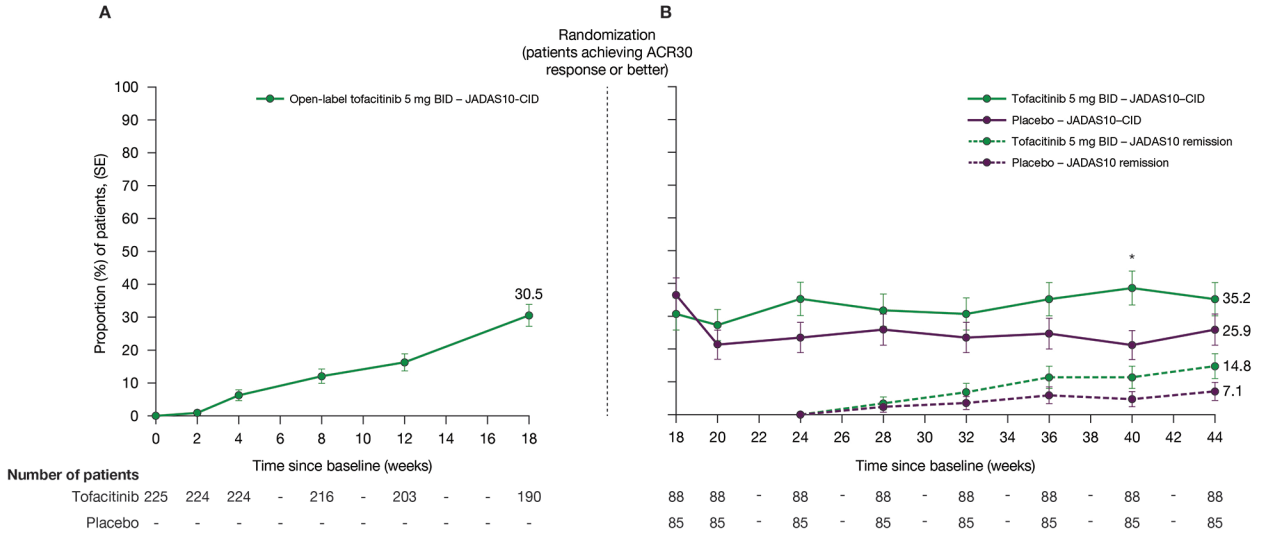

Figure 3. Patients achieving JADAS10-CID[a] or remission[b] (ie, ≥ 24 continuous weeks of JADAS10-CID) in (A) part 1 (all enrolled patients) and (B) part 2 (patients randomized to either tofacitinib[c] or placebo). A missing binary response prior to discontinuation during part 1 or part 2 was imputed using last observation carried forward. There was no imputation of missing data for patients who discontinued treatment for any reason during part 1. Patients who discontinued treatment for any reason during part 2, except while in clinical remission, were categorized as CID ("no") as of their discontinuation visit through to week 44. * $P < 0.05$ for tofacitinib vs placebo ($P = 0.01$, 95% CI for difference in proportions 4.08-30.84). At week 44, $P = 0.18$ for tofacitinib vs placebo (95% CI for difference in proportions −4.30 to 22.99). [a] JADAS10-CID was defined as JADAS10 score of ≤ 2.7 for patients with polyarthritis and ≤ 1.4 for patients with oligoarthritis.[12] [b] Clinical remission was defined as ≥ 24 continuous weeks of JADAS10-CID. [c] Tofacitinib 5 mg BID or equivalent weight-based lower dose in patients < 40 kg. ACR30: American College of Rheumatology improvement by ≥ 30%; BID: twice daily; CID: clinically inactive disease; JADAS10: Juvenile Arthritis Disease Activity Score in 10 joints, based on C-reactive protein; SE: standard error.

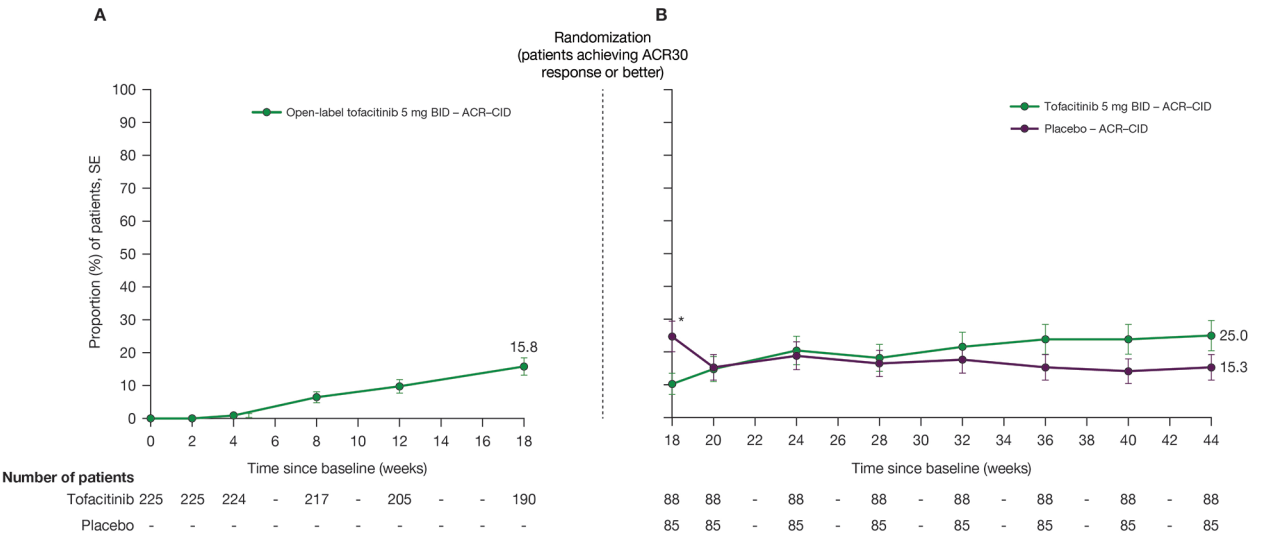

Figure 4. Patients achieving ACR-CID[a] in (A) part 1 (all enrolled patients) and (B) part 2 (patients randomized to either tofacitinib[b] or placebo). A missing binary response prior to discontinuation during part 1 or part 2 was imputed using last observation carried forward. There was no imputation of missing data for patients who discontinued treatment for any reason during part 1. Patients who discontinued treatment for any reason during part 2, except while in clinical remission, were categorized as CID ("no") as of their discontinuation visit through to week 44. * $P < 0.05$ at week 18 for tofacitinib vs placebo ($P = 0.01$, 95% CI for difference in proportions −25.62 to −3.34). At week 44, $P = 0.11$ for tofacitinib vs placebo (95% CI for difference in proportions −2.14 to 21.56). [a] ACR-CID was defined as no joints with active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; erythrocyte sedimentation rate or C-reactive protein level within normal limits in the laboratory (where tested) or, if elevated, not attributable to JIA; best possible physician global assessment of disease activity score on the scale used; and duration of morning stiffness ≤ 15 minutes.[10] [b] Tofacitinib 5 mg BID or equivalent weight-based lower dose in patients < 40 kg. ACR30: American College of Rheumatology improvement by ≥ 30%; ACR-CID: ACR-defined clinically inactive disease; BID: twice daily; JIA: juvenile idiopathic arthritis; SE: standard error.

From week 32 onward, rates of ACR-CID were numerically higher with tofacitinib compared with placebo (Figure 4B). The number of patients achieving ACR clinical remission during part 2 was low (4 patients receiving tofacitinib and 3 patients receiving placebo).

When normal physical function was assessed in combination with ACR-CID, similar trends were observed compared to ACR-CID assessed alone; ACR-CID plus normal physical function steadily increased throughout part 1 and was achieved by 9% (17/190) of patients at the end of part 1. Subsequently, in part 2, the proportion of patients achieving this outcome in the tofacitinib group increased over time (up to 20.5% [18/88] at week 44), whereas in the placebo group, the proportion of patients achieving this outcome remained stable over time (to 10.6% [9/85] at week 44; Supplementary Figure S2, available with the online version of this article).

DISCUSSION

In these post hoc analyses, we examined CID and remission following tofacitinib treatment using the 2021 JADAS10 threshold scores for patients with polyarthritis.[12] Treatment with tofacitinib rapidly reduced disease activity over time in patients with JIA, with mean values decreasing from JADAS10-HDA at baseline to the lower bound of JADAS10-MoDA at week 18 and reaching JADAS10-MiDA by week 44. In the analysis of observed scores, approximately half of the patients remaining in both treatment groups at week 44 had achieved JADAS10-CID. When imputation was applied to the binary outcome after discontinuation, approximately one-third (for tofacitinib) or one-quarter (for placebo) of patients met the requirements for CID by week 44. The maintenance of CID in a proportion of patients who switched to placebo suggests that the use of tofacitinib results in continuous disease control over time for some patients.

As expected, rates of JADAS10-CID and remission were consistently numerically higher in patients treated with tofacitinib than in patients treated with placebo throughout part 2 of the study (imputed binary outcome after discontinuation). Nevertheless, JADAS10 remission rates during part 2 were relatively low, although this may have been affected by the short duration of the study and the sustained symptom control required. These findings suggest that JADAS10-CID is a feasible treatment target for patients with JIA treated with tofacitinib.

In comparison with ACR-CID, rates of JADAS10-CID were higher, which is in line with expectations, given that the ACR criteria are stricter, with patients having to achieve additional criteria. Moreover, whereas rates of JADAS10-CID were maintained throughout part 2, rates of ACR-CID continued to steadily increase up to 25% in the group receiving tofacitinib at week 44. The rates of ACR-CID observed are comparable with a previous study of JIA in patients receiving double-blind treatment with abatacept.[21] Interestingly, rates of CID in our analysis were lower than in studies of patients receiving etanercept[22] or open-label treatment with golimumab.[23] This may be accounted for by the age at disease onset; the study of etanercept found that children (median age 3.6 years) with disease onset before 3.6 years of age had a greater likelihood of achieving ACR-CID.[22] By comparison, patients in our analysis were older at disease onset (median age 8 years).

Moreover, compared with the primary results from the phase III trial—which assessed inactive disease in polyarticular-course JIA using JADAS27 based on CRP, according to the 2012-2014 JADAS threshold score of ≤ 1 for patients with polyarthritis[14]—the percentage of patients with JIA achieving CID was higher in the current analysis (using JADAS10-CRP based on the 2021 threshold score of ≤ 2.7[12]): 35.2% vs 18% at week 44, respectively. This is unsurprising, given the slightly less stringent 2021 thresholds for CID. Correspondingly, a study investigating the performance of JADAS10 thresholds demonstrated that the 2021 thresholds for polyarthritis resulted in a higher proportion of patients classified as having minimal disease activity compared with the 2012-2014 cutoffs.[24]

Throughout part 1 and part 2 in the tofacitinib and placebo groups, trends observed for JADAS10-CID or remission were mostly similar when assessed in combination with normal physical function. However, in part 2, the rate of JADAS10-CID plus normal physical function—a stricter endpoint—increased over time in the tofacitinib group, reaching a rate of more than one-quarter of patients, whereas the rate of CID alone remained relatively constant. It should be noted that in clinical practice, other modalities such as physiotherapy may assist patients in achieving normal physical function, as deemed appropriate. In the current study, patients could have continued, added, or removed nonpharmacologic therapies, although concomitant physiotherapy was reported for only 2 patients.

Limitations of this study include the post hoc nature of the analyses and the small sample size of the trial population. In addition, CID status may have been overestimated by JADAS10-CRP. Tofacitinib has been shown to target the interleukin 6 (IL-6) pathway, which is strongly correlated with circulating CRP levels.[25,26] Although CRP levels are widely used for monitoring disease activity in rheumatoid arthritis, there may be challenges in assessing disease activity with JADAS10-CRP in patients receiving treatments that inhibit IL-6, as reductions in CRP may not directly correspond with CID.[25,26] It should also be considered that the 2021 JADAS10 thresholds[12] for CID and remission have not been validated for patients with RF-positive polyarthritis, PsA, or ERA.[24] Moreover, observed differences between tofacitinib and placebo efficacy may have been reduced by the large number of placebo-treated patients who discontinued in part 2 compared with tofacitinib (55.3% vs 30.7%, respectively; primarily due to JIA flare[18]). It can be surmised that the placebo-treated patients who remained in the study may have had less severe disease activity, and thus observed-case data should be interpreted with caution. A final limitation to note is that the follow-up time may not have been sufficient for optimal assessment of remission.

In conclusion, in patients with JIA who had extended oligoarthritis, RF-positive or RF-negative polyarthritis, sJIA without systemic features, PsA, or ERA, as well as active disease at baseline, disease activity was reduced with tofacitinib treatment in a rapid manner and was sustained over time. Rates of

CID, based on the 2021 JADAS10 thresholds and ACR criteria, were sustained throughout part 2 in patients treated with tofacitinib and decreased early in part 2 when patients switched to placebo. The rates of CID followed similar trends based on JADAS10 and ACR criteria, although rates were higher and stabilized earlier for JADAS10-CID compared with ACR-CID. A small proportion of patients receiving tofacitinib or placebo achieved JADAS10 remission in part 2. Taken together, these results suggest that CID (based on JADAS10 or ACR criteria) and remission (based on JADAS10 criteria) are feasible treatment targets in patients receiving tofacitinib The efficacy results presented here will further inform clinical decision making in regard to tofacitinib as an oral treatment option for patients with JIA.

ACKNOWLEDGMENT

We thank the participating centers, the families of the patients with juvenile idiopathic arthritis, and the research assistants at the PRINTO and PRCSG coordinating centers for their remote and independent evaluation of the data. We would also like to thank the late Dr. Ricardo M. Suehiro for his contributions to the data and analyses. Medical writing support, under the direction of the authors, was provided by Lauren Hogarth, MSc, CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer, New York, New York, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (Ann Intern Med 2022;175:1298-304).

CONTRIBUTIONS

Conceptualization and design of study: AC, DJL, LS, and NR. Data acquisition: DJL, OS, CAM, AS, YV, EA, PC, IL, NR, and HIB. Data analysis: AC, DJL, IL, MJC, and NR. Data interpretation: AC, NR, DJL, OS, CAM, AS, YV, EA, JC, PC, IL, LS, MJC, AD, and HIB. All authors were involved in drafting the article or reviewing it critically for important intellectual content. All authors read and gave approval of the final version submitted for publication and accept accountability for the accuracy and integrity of the work. The phase III trial was designed jointly by the study sponsor (Pfizer Inc.) and PRINTO/PRCSG officers (NR, DJL, HIB, and Alberto Martini). The sponsor was responsible for the overall management of the study and the data analysis. This post hoc analysis was conceived by the sponsor in collaboration with the academic authors; data were generated by the sponsor. All authors had access to the data and were involved in the interpretation of data for this report.

FUNDING

This study was sponsored by Pfizer Inc.

COMPETING INTERESTS

AC has received research grants from Alfasigma and Pfizer Inc. NR has been a consultant or member of the speakers' bureau for AbbVie, Aclaris, AlfaSigma, Amgen, AstraZeneca, Aurinia, Boehringer Ingelheim, BMS, Eli Lilly, Galapagos, Guidepoint, Idorsia, Janssen, Novartis, Pfizer Inc., Roche Genentech, Sanofi, and Takeda. DJL has received research grants/support from BMS, Janssen, Novartis, Pfizer Inc., Roche, and UCB; is a consultant for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Pfizer Inc., Roche, Takeda, and UCB; is a Data Safety Monitoring Board member for the National Institutes of Health; and is a member of the speakers' bureau for Novartis and Roche. OS is a member of the speakers' bureau for Alpen, Krka, and Sanofi. CAM has been a consultant and member of the speakers' bureau for AbbVie and GSK. AS is a member of the speakers' bureau for Eli Lilly. EA has received research grants/support from AbbVie, Amgen, BMS, Centocor, Eli Lilly, MSD, Novartis, Pfizer Inc., Roche, and Sanofi, and is a member of the speakers' bureau for AbbVie, BMS, MSD, Novartis, Pfizer Inc., and Roche. PC has received research grants/support from Pfizer Inc. and is a consultant for CARRA and Novartis. IL is an employee of IQVIA, who were paid contractors to Pfizer in the development of this manuscript and provided statistical support. LS, MJC, and AD are employees and shareholders of Pfizer Inc. HIB has received research grants/support from BMS, MedImmune, Novartis, and Pfizer Inc.; is a consultant for AbbVie, AstraZeneca-MedImmune, Bayer, Biocon, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, Novartis, Pfizer Inc., Roche, and R-Pharm; and is a member of the speakers' bureau for GSK, Novartis, and Roche. YV and JC have no conflicts to disclose.

ETHICS AND PATIENT CONSENT

The trial was conducted in accordance with the Guidelines for Good Clinical Practice of the International Council for Harmonisation, the Declaration of Helsinki, and local regulatory requirements and laws, and was approved by Institutional Review Boards or Ethics Committees at all sites. Written informed consent or assent was provided by parents, legal guardians, or patients.

DATA AVAILABILITY

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

SUPPLEMENTARY DATA

Supplementary material accompanies the online version of this article.

REFERENCES

1. Brunner HI, Chen C, Bovis F, et al. Functional ability and health-related quality of life in randomized controlled trials of tocilizumab in patients with juvenile idiopathic arthritis. Arthritis Care Res 2021;73:1264-74.
2. Consolaro A, Giancane G, Alongi A, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. Lancet Child Adolesc Health 2019;3:255-63.
3. Martini A, Lovell DJ, Albani S, et al. Juvenile idiopathic arthritis. Nat Rev Dis Primers 2022;8:5.
4. Seid M, Opipari L, Huang B, Brunner HI, Lovell DJ. Disease control and health-related quality of life in juvenile idiopathic arthritis. Arthritis Rheum 2009;61:393-9.
5. Magni-Manzoni S, Ruperto N, Pistorio A, et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum 2008;59:1120-7.
6. Klein A, Minden K, Hospach A, et al. Treat-to-target study for improved outcome in polyarticular juvenile idiopathic arthritis. Ann Rheum Dis 2020;79:969-74.
7. Ravelli A, Consolaro A, Horneff G, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis 2018;77:819-28.
8. Consolaro A, Giancane G, Schiappapietra B, et al. Clinical outcome measures in juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2016;14:23.
9. Consolaro A, Ruperto N, Bazso A, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009;61:658-66.
10. Wallace CA, Giannini EH, Huang B, et al. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res 2011;63:929-36.
11. Wallace CA, Ruperto N, Giannini E, Childhood Arthritis and Rheumatology Research Alliance, Pediatric Rheumatology International Trials Organ, Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290-4.

12. Trincianti C, Van Dijkhuizen EHP, Alongi A, et al. Definition and validation of the American College of Rheumatology 2021 Juvenile Arthritis Disease Activity Score cutoffs for disease activity states in juvenile idiopathic arthritis. Arthritis Rheumatol 2021;73:1966-75.
13. Ruperto N, Brunner HI, Zuber Z, et al. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study. Pediatr Rheumatol Online J 2017;15:86.
14. Ruperto N, Brunner HI, Synoverska O, et al. Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial. Lancet 2021;398:1984-96.
15. Ruperto N, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). Arch Dis Child 2011;96:596-601.
16. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
17. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.
18. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. J Rheumatol 2002;29:1058-64.
19. Nordal EB, Zak M, Aalto K, et al. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. Ann Rheum Dis 2012;71:1122-7.
20. Ruperto N, Ravelli A, Pistorio A, et al. Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin Exp Rheumatol 2001;19 Suppl 23:S1-9.
21. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008;372:383-91.
22. Solari N, Palmisani E, Consolaro A, et al. Factors associated with achievement of inactive disease in children with juvenile idiopathic arthritis treated with etanercept. J Rheumatol 2013;40:192-200.
23. Brunner HI, Ruperto N, Tzaribachev N, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis 2018;77:21-9.
24. Backström M, Salo H, Kärki J, et al. The feasibility of existing JADAS10 cut-off values in clinical practice: a study of data from the Finnish Rheumatology Quality Register. Pediatr Rheumatol Online J 2023;21:35.
25. Frade-Sosa B, Ponce A, Ruiz-Esquide V, et al. High sensitivity C reactive protein in patients with rheumatoid arthritis treated with antibodies against IL-6 or Jak inhibitors: a clinical and ultrasonographic study. Diagnostics 2022;12:182.
26. Pope JE, Choy EH. C-reactive protein and implications in rheumatoid arthritis and associated comorbidities. Semin Arthritis Rheum 2021;51:219-29.