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Tofacitinib for the Treatment of Juvenile Idiopathic Arthritis: Patient-Reported Outcomes in a Phase 3, Randomized, Double-Blind, Placebo-Controlled Withdrawal Trial

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Objective. Juvenile idiopathic arthritis (JIA) is associated with impaired overall health-related quality of life (HRQoL). We evaluated the impact of tofacitinib on patient-reported outcomes (PROs) in patients with JIA.

Methods. This was a post hoc analysis of a phase 3, randomized, double-blind, placebo-controlled withdrawal trial (NCT02592434) in patients with JIA. In the open-label phase (part 1; weeks 0–18), patients received body weight–based doses of tofacitinib. During the double-blind phase (part 2; weeks 18–44), responders (per JIA-American College of Rheumatology 30 response criteria) were randomized 1:1 to continue tofacitinib or switch to placebo for up to 26 weeks. Assessed PROs included the validated parent and/or legal guardian versions of the Childhood Health Assessment Questionnaire for evaluation of disability, arthritis pain, overall well-being, and the Child Health Questionnaire (CHQ).

Results. Overall, 225 patients were enrolled and received open-label tofacitinib in part 1, and 173 patients were randomized in part 2. During part 1, least-squares (LS) mean (SE) disability, arthritis pain, and overall well-being scores numerically improved from mean 1.04 (SE 0.05), mean 5.53 (SE 0.20), and mean 5.07 (SE 0.20) at baseline to mean 0.57 (SE 0.05), mean 2.46 (SE 0.18), and mean 2.47 (SE 0.18) at week 18, respectively. LS mean (SE) CHQ physical summary and psychological summary scores numerically improved from mean 29.51 (SE 1.15) and mean 47.24 (SE 0.85) at baseline to mean 42.70 (SE 0.98) and mean 51.53 (SE 0.80) at week 18, respectively. Improvements were generally maintained to week 44 in part 2.

Conclusion. Tofacitinib improved a range of PROs in patients with JIA, suggesting potential HRQoL benefits.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is associated with pain, poor physical functioning, and considerable impairment of overall health-related quality of life (HRQoL).[1–12] Besides improvement of articular involvement and other core measures of JIA, key goals of treatment are the improvement of patient HRQoL, including improving physical function, physical and psychological well-

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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.

being, and reducing pain.[13–15] Such outcomes are generally referred to as patient-reported outcomes (PROs) and provide unique information on the impact of a medical condition and its treatment that are important to the patient.

In 1997, a core set of six JIA outcome variables was identified, which included two PROs (parent and patient assessment of overall well-being and functional ability). From this core set, a definition of clinically important improvement was derived with the aim of promoting a single efficacy measure in JIA trials,[14] which was later endorsed by the American College of Rheumatology (ACR; JIA-ACR response criteria)[14] and regulatory agencies. In 2016, this definition was re-evaluated and updated with input from patients and parents in which pain was added to the core set.[15] Encouraged by regulatory authorities,[16] the inclusion of PROs in clinical trials has increased over time,[17] and assessment of HRQoL and other PRO measures is considered essential to fully assess the benefits of JIA treatments in both research and routine clinical care.[18,19] PROs in children and adolescents can be collected from either the patient or the parent and/or legal guardian (parent-proxy report).[19,20]

Tofacitinib is an oral JAK inhibitor for the treatment of patients with polyarticular course JIA (pcJIA) and juvenile psoriatic arthritis (jPsA)[21,22] and is currently being investigated for systemic JIA (sJIA).[23] In this post hoc analysis, we report a comprehensive assessment of the impact of tofacitinib on a range of PROs in a phase 3, 44-week clinical trial conducted in patients with JIA.

PATIENTS AND METHODS

Trial design and patients. Key details of the trial design and patient inclusion and exclusion criteria were reported previously.[24] Briefly, this was a phase 3, randomized, double-blind, placebo-controlled withdrawal trial (ClinicalTrials.gov NCT02592434). In the open-label run-in phase (part 1; weeks 0–18), patients received body weight–based doses of tofacitinib (5 mg tablets twice daily or oral formulations as appropriate).[24] During the double-blind phase (part 2; weeks 18–44), patients meeting the JIA-ACR 30 response criteria were randomized 1:1 to continue tofacitinib or switch to placebo for up to an additional 26 weeks. Patients who experienced a JIA flare during the open-label or double-blind phases were discontinued from the trial. Following completion of this trial (or discontinuation for reasons other than treatment-related serious adverse events), patients could enroll in a long-term extension (LTE) study of open-label tofacitinib (NCT01500551).

Eligible patients were aged 2 to 18 years old, met the International League of Associations for Rheumatology JIA classification criteria[25] for any of the following JIA categories grouped under the functional concept of pcJIA (≥5 active joints at enrollment): extended oligoarthritis, rheumatoid factor (RF)+ or RF– polyarthritis, sJIA without systemic features 6 months or more before enrollment, jPsA or enthesitis-related arthritis (ERA; ≥3 active joints at enrollment), and had an inadequate response to one or more disease-modifying antirheumatic drug (DMARD; methotrexate [MTX], or biologic DMARDs [bDMARDs]). The study was sponsored by Pfizer, which manufactures tofacitinib. The trial was designed jointly by Paediatric Rheumatology International Trials Organisation (PRINTO)/Pediatric Rheumatology Collaborative Study Group (PRCSG) investigators and the sponsor, and data were collected by the PRINTO/PRCSG investigators. Data from this trial were used by the sponsor to support the marketing approval of tofacitinib.

This trial was conducted in accordance with the International Council on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and local regulatory requirements and laws. The final protocol, any amendments, and informed consent documents were reviewed and approved by the institutional review board or independent ethics committee at every center. Parents, legal guardians, and patients provided written informed consent and assent when required by local institutional review boards and independent ethics committees before performing any study-related activities.

Assessment of PROs. PRO assessments were completed by the parent and/or legal guardian but could be completed by the patient if they were aged ≥14 years and able to complete the assessment correctly and consistently for the duration of the study. Disability, arthritis pain, and patient overall well-being were assessed as part of the Childhood Health Assessment Questionnaire (CHAQ), administered at each visit (baseline and weeks 2, 4, 8, 12, 18, 20, 24, 28, 32, 36, 40, and 44). Disability was assessed by measuring physical function impairment using the CHAQ-Disability Index (CHAQ-DI); scores could range from 0 to 3, with higher scores indicating more disability. Arthritis pain (CHAQ-Discomfort Index) and patient overall well-being were assessed on a 21-circle visual analog scale (VAS); scores could range from 0 to 10, with higher scores indicating more arthritis pain or worse well-being, as appropriate. Additionally, duration of morning stiffness (minutes) was collected at each visit. HRQoL was assessed at baseline and weeks 18 and 44 by the Child Health Questionnaire (CHQ), which includes ratings for 15 CHQ health concepts that can be summarized in physical summary (PhS) and psychosocial summary (PsS) scores; each of the 15 health concept scores could range from 0 to 100

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(with the exception of change in health, ranging from 1–5), with higher scores indicating better physical function or mental health, as appropriate. CHQ PhS and PsS scores were standardized to have a mean (SD) of 50 (±10) in a normative population of US children.[5,26] The cross-culturally adapted and validated national language versions of the CHAQ (parent and/or legal guardian version) and CHQ-parent form 50 were used.[11] For patients with ERA, overall back pain and nocturnal back pain were also measured at each visit.

Rates of patients achieving minimal clinically important differences (MCID) in CHAQ-DI (score reduction of ≥0.188),[27] minimal arthritis pain (CHAQ-Discomfort Index score of ≤0.35), or no disability status (CHAQ-DI = 0) were also assessed. Additional details on the PROs assessed in this analysis are summarized in the Supplementary Materials.

Physician-reported outcome assessments. In addition to the assessment of PROs, Physician Global Assessment (PGA) and the number of joints with active arthritis were also assessed at each visit. PGA was assessed on a 10-cm VAS with scores ranging from 0 (no disease activity) to 10 (maximum disease activity). The number of joints with active arthritis was identified using the JIA-ACR definition: any joint with swelling or, in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity (range 0–71).

Statistical analysis. Descriptive statistics are provided for selected characteristics of the part 1 baseline values. Mixed-effects linear models were fit using PROC MIXED in SAS version 9.4. For part 1 of the study, the model included the effects of the week (postbaseline, at visits where the dependent variable was measured), baseline C-reactive protein (categorized as normal or above normal), patient population and/or group (overall, pcJIA, jPsA, and ERA), and baseline value of the dependent variable; patients were a random effect. Least-squares (LS) means for each outcome were assessed at each timepoint and are reported. For part 2 of the study, the model was the same as part 1, except with the addition of treatment group and an interaction term of treatment with the effect of week. LS means were analyzed with a longitudinal mixed-effects model. *P* values for the difference between the treatment arms in part 2 at each timepoint were provided for all PROs, except CHQ health concepts. The rate of patients achieving MCID in CHAQ-DI, minimal arthritis pain, or no disability status were analyzed by visit using the normal approximation approach for binomial populations. A Kruskal-Wallis test was performed by visit to assess whether distributions of the data between treatment arms were significantly different (medians, interquartile ranges, and *P* values for these tests are reported in the Supplementary Materials). Because these are post hoc analyses, *P* values were provided to indicate the strength in the degree of change in the outcomes and are not for hypothesis testing. Analyses of PROs were based on observed data without imputation for missing values; patients who discontinued from the study due to JIA flares or other reasons were not analyzed at subsequent timepoints. The number of patients with available data at each timepoint is reported for each PRO. Analyses of PGA and the number of joints with active arthritis were descriptive.

RESULTS

Patients. Overall, 225 patients were enrolled and received open-label tofacitinib in part 1 (pcJIA, N = 184; jPsA, N = 20; ERA, N = 21). A total of 173 patients who enrolled in part 1 were subsequently randomized in part 2, including 142 patients with pcJIA (tofacitinib, n = 72; placebo, n = 70), 15 patients with jPsA (tofacitinib, n = 7; placebo, n = 8), and 16 patients with ERA (tofacitinib, n = 9; placebo, n = 7).

The majority of patients enrolled in part 1 of the study were girls (75.1%), aged 12 to 18 years (61.8%), White (87.1%), and weighed ≥40 kg (62.7%). At baseline, the scores (25th percentile [Q1], 75th percentile [Q3]) were median 0.9 (Q1 0.3, Q3 1.5) for CHAQ-DI, median 6.0 (Q1 3.5, Q3 7.0) for arthritis pain, and median 5.0 (Q1 3.0, Q3 7.0) for patient overall well-being (Table 1).

Baseline scores of PROs for individual pcJIA, jPsA, and ERA groups are reported within Supplementary Table 1. Part 1 baseline PRO scores for patients randomized to part 2, overall and by JIA category, are summarized in Supplementary Table 2.

Changes in PROs during part 1. During part 1 in the overall population, continued improvements in patient disability, pain, and overall well-being were observed through to week 18. LS mean CHAQ-DI scores (Figure 1), arthritis pain scores (Figure 2), and patient overall well-being scores (Figure 3) numerically improved from baseline to week 18. At week 18, the rate of achieving MCID in CHAQ-DI was 48.0% (SE 3.33; Supplementary Figure 1). The proportion of patients with no disability (CHAQ-DI = 0) generally increased over time from 12.9% (SE 2.2) at baseline to 28.0% (SE 3.0) at week 18 (Supplementary Figure 2A). The proportion of patients achieving minimal arthritis pain (CHAQ-Discomfort Index score of ≤0.35) generally increased during part 1 from 4.4% (SE 1.4) at baseline to 15.6% (SE 2.4) at week 18 (Supplementary Figure 3A).

LS mean scores for patient disability, arthritis pain, and overall well-being in pcJIA, jPsA, and ERA groups are shown in Supplementary Figures 4 to 6. The rates of achieving MCID in CHAQ-DI, proportion of patients achieving no disability, and proportion of patients achieving minimal arthritis pain in the pcJIA, jPsA, and ERA groups are reported in Supplementary Figures 1, 2B to 2D, and 3B to 3D, respectively.

In the overall population, numerical improvements from baseline in both CHQ PhS and PsS scores were observed at week 18 (Figure 4A). The greatest improvements were observed

Table 1. Patient characteristics and baseline patient-reported outcomes for patients with juvenile idiopathic arthritis receiving tofacitinib in part 1 (overall population)*

Characteristics	Overall (N = 225)
Patient characteristics	
Female sex, n (%)	169 (75.1)
Age, median (Q1, Q3), years	13.0 (9.0, 15.0)
Disease duration, median (Q1, Q3), years	2.5 (1.0, 5.6)
Patient-reported outcomes, median (Q1, Q3)	
CHAQ-DI score	0.9 (0.3, 1.5)
Arthritis pain	6.0 (3.5, 7.0)
Patient overall well-being	5.0 (3.0, 7.0)
CHQ physical summary score	30.6 (19.6, 42.6)
CHQ psychosocial summary score	48.2 (40.6, 56.6)
CHQ health concepts	
Global health	60.0 (30.0, 60.0)
Physical function	66.7 (38.9, 88.9)
Social limitations–physical	66.7 (33.3, 100.0)
Social limitations–emotional	88.9 (44.4, 100.0)
Bodily pain	40.0 (20.0, 60.0)
Behavior	79.2 (64.2, 89.2)
Global behavior	85.0 (60.0, 85.0)
Mental health	70.0 (55.0, 80.0)
Self-esteem	75.0 (62.5, 87.5)
General health	51.7 (42.5, 60.0)
Change in health	3.0 (2.0, 4.0)
Parental emotional impact	58.3 (33.3, 75.0)
Parental time impact	77.8 (55.6, 100.0)
Family activity	79.2 (62.5, 95.8)
Family cohesion	85.0 (60.0, 85.0)
Duration of morning stiffness, minutes	30.0 (15.0, 60.0)
Physician-reported outcomes, median (Q1, Q3)	
PGA	6.0 (4.5, 7.5)
Number of joints with active arthritis	10.0 (6.0, 15.0)

* CHAQ-DI, Childhood Health Assessment Questionnaire-Disability Index; CHQ, Child Health Questionnaire; PGA, Physician Global Assessment of Overall Disease Activity; Q1, 25th percentile; Q3, 75th percentile.

in CHQ PhS, which improved from approximately 2 SDs below the standardized mean score of 50 for a normative population to within the range of the normative population (Figure 4A); mean PsS scores remained within the range of the normative population at baseline and week 18. LS mean scores for CHQ PhS and PsS for the pcJIA, jPsA, and ERA groups are shown in Supplementary Figure 7.

The LS mean values of the 15 CHQ health concepts scores at baseline and week 18 for the overall population are shown in Figure 4B. At the end of part 1, numerical improvements from baseline were generally observed with tofacitinib across all CHQ health concepts. The greatest improvement was observed in bodily pain, which improved from 40.05 at baseline to 70.54 at week 18. Substantial improvements from baseline were also observed in global health (baseline 47.32, week 18 68.09), physical function (baseline 58.33, week 18 79.30), and role and social limitations–physical (baseline 62.75, week 18 83.44). LS mean values of the 15 CHQ health concepts for pcJIA, jPsA, and ERA groups are shown in Supplementary Figure 8A to 8C.

A numerical reduction in the duration of morning stiffness was observed during part 1 in the overall population (Figure 5). Changes in the duration of morning stiffness for pcJIA, jPsA, and ERA groups, as well as changes in average back pain and nocturnal back pain in the ERA group, are reported in Supplementary Figure 9 and Supplementary Figure 10, respectively.

Changes in PROs during part 2. In the overall population, improvements in PROs achieved at the end of part 1 were generally maintained throughout part 2, although some differences were observed between the two treatment arms. Disability scores (LS mean) were generally maintained throughout part 2, consistent with part 2 baseline (week 18) values for both treatment arms (Figure 1). Throughout part 2, arthritis pain scores generally remained stable and consistent with part 2 baseline values, although patients receiving tofacitinib demonstrated lower ($P < 0.05$) arthritis pain scores compared with patients receiving placebo at week 28 (Figure 2). Patient overall well-being scores remained consistent with part 2 baseline values throughout part 2 in patients receiving tofacitinib (Figure 3). Patients receiving tofacitinib generally demonstrated similar overall well-being scores compared with those receiving placebo; however, scores were lower (indicating greater well-being) in the tofacitinib group at week 24 and week 32 (both $P < 0.05$).

In general, the proportion of patients achieving no disability (CHAQ = 0) in the overall population numerically improved throughout part 2 in patients receiving tofacitinib (week 18, proportion 33.0%, SE 5.0; week 44, proportion 38.6%, SE 5.2) but numerically declined in patients receiving placebo (week 18, proportion 40.0%, SE 5.3; week 44, proportion 23.5%, SE 4.6; Supplementary Figure 2A). A higher ($P < 0.05$) proportion of patients receiving tofacitinib achieved no disability compared with patients receiving placebo at week 36 (proportion 37.5%, SE 5.2 vs proportion 23.5%, SE 4.6) and week 44 (proportion 38.6%, SE 5.2 vs proportion 23.5%, SE 4.6). The proportion of patients with minimal arthritis pain generally remained stable throughout part 2 in patients receiving tofacitinib, whereas a numerically higher proportion of patients achieved minimal arthritis pain at week 44 (proportion 26.1%, SE 4.7) compared with part 2 baseline (proportion 20.5%, SE 4.3; Supplementary Figure 3A). The proportion of patients receiving placebo and achieving minimal arthritis pain generally declined during part 2 from 20.0% (SE 4.3) at baseline to 11.8% (SE 3.5) at week 44 (Supplementary Figure 3A). A higher proportion of patients achieved minimal arthritis pain in the tofacitinib group than in the placebo group at week 28 (proportion 23.9, SE 4.5 vs proportion 8.2, SE 3.0; $P < 0.01$), week 32 (proportion 22.7, SE 4.5 vs proportion 7.1, SE 2.8; $P < 0.01$), week 40 (proportion 28.4, SE 4.8 vs proportion 12.9, SE 3.6; $P < 0.05$), and week 44 (proportion 26.1, SE 4.7 vs proportion 11.8, SE 3.5; $P < 0.05$).

Improvements in CHQ PhS and PsS scores (LS means) in the overall population were maintained at part 2 baseline

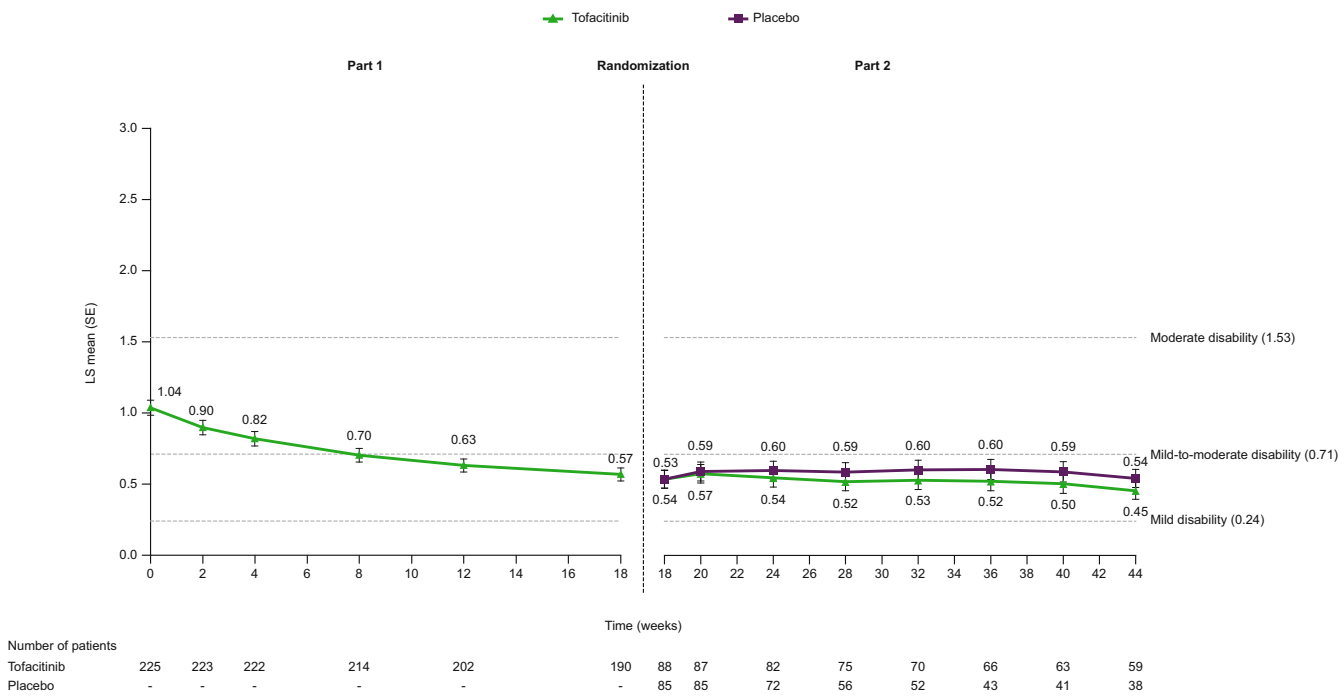

Figure 1. LS mean (±SE) Childhood Health Assessment Questionnaire-Disability Index scores over time in patients with juvenile idiopathic arthritis treated with tofacitinib in part 1 and tofacitinib or placebo in part 2 (overall population). Analyses were based on observed data; missing values were not imputed. Horizontal dashed lines represent mean Childhood Health Assessment Questionnaire-Disability Index scores for patients with mild, mild-to-moderate, and moderate disability, which have been previously reported.[28] Vertical dashed line represents randomization (patients meeting the juvenile idiopathic arthritis American College of Rheumatology 30 response criteria randomized 1:1 to continue tofacitinib or switch to placebo for up to an additional 26 weeks). Median and interquartile range values for Childhood Health Assessment Questionnaire-Disability Index are summarized in Supplementary Table 3; no significant differences in the distributions between the treatment arms were observed during part 2. LS, least-squares.

levels through to week 44 and were similar between patients receiving tofacitinib and those receiving placebo (Figure 4). At week 44, most CHQ health concept scores (LS means) were either maintained at part 2 baseline values or showed further numerical improvement regardless of treatment arm (Figure 4B).

There was a small numerical increase in the duration of morning stiffness during part 2 for patients receiving both tofacitinib and placebo (Figure 5). Patients receiving tofacitinib demonstrated a shorter duration of morning stiffness at week 28 compared with those receiving placebo ($P < 0.05$). Part 2 data for pcJIA, jPsA, and ERA groups are presented within the Supplementary Materials.

Physician-reported outcomes in parts 1 and 2. In the overall population, both the PGA scores and the number of joints with active arthritis demonstrated a similar pattern of improvement to that observed with the PROs. During part 1, the mean PGA score decreased from 6.18 (SD 1.88) at baseline to 1.68 (SD 1.66) at week 18 (Supplementary Figure 11A). Similarly, the mean number of joints with active arthritis decreased from 12.23 (SD 8.11) at baseline to 1.94 (SD 3.73) at week 18 (Supplementary Figure 12A).

During part 2 of the study, PGA scores and the number of joints with active arthritis were similar between both treatment arms and remained consistent with part 2 baseline values throughout the observation period (Supplementary Figures 11A and 12A). Data for pcJIA, jPsA, and ERA groups are presented within Supplementary Figures 11B to 11D and 12B to 12D.

DISCUSSION

The efficacy of tofacitinib versus placebo to improve JIA signs and symptoms has previously been demonstrated in a phase 3 study in patients with JIA.[24] HRQoL assessments highlight aspects of disease that are important to the patient but may not be captured by standard clinical assessments. In this post hoc analysis, we observed improvements in a range of PROs and two physician-reported effectiveness outcomes in patients with JIA receiving open-label tofacitinib during part 1 of the study.

When patients were randomized to tofacitinib or placebo in part 2, both treatment arms generally maintained these improvements or showed further numerical improvements with tofacitinib versus placebo across several PROs. Improvements in PROs were also observed in all JIA subgroups studied. Although the general trends of improvement observed in the jPsA and ERA

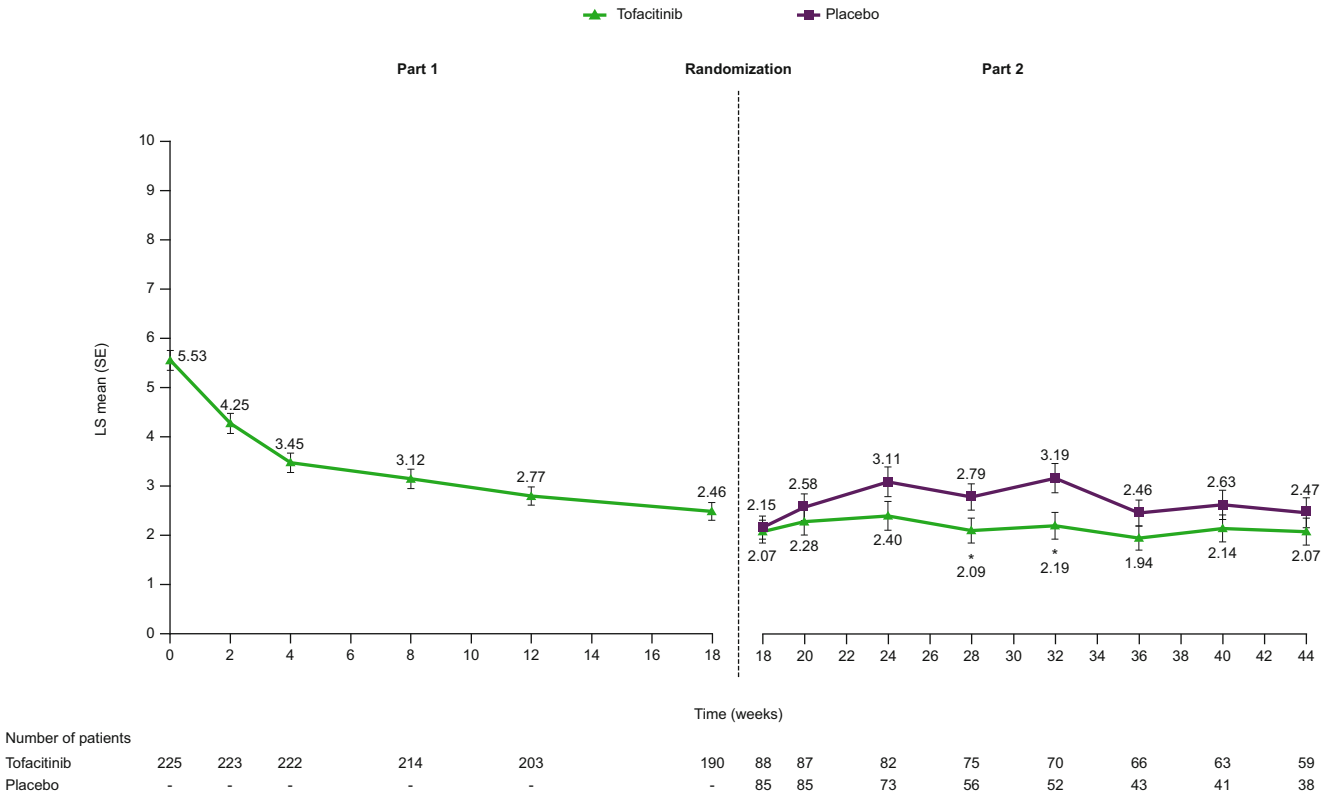

Figure 2. LS mean (±SE) arthritis pain (Childhood Health Assessment Questionnaire-Discomfort Index) scores over time in patients with juvenile idiopathic arthritis treated with tofacitinib in part 1 and tofacitinib or placebo in part 2 (overall population). *$P < 0.05$ vs placebo. Analyses were based on observed data; missing values were not imputed. Dashed line represents randomization (patients meeting the juvenile idiopathic arthritis American College of Rheumatology 30 response criteria randomized 1:1 to continue tofacitinib or switch to placebo for up to an additional 26 weeks). Median and interquartile range values for arthritis pain (Childhood Health Assessment Questionnaire-Discomfort Index) scores are summarized in Supplementary Table 3; significant differences ($P < 0.05$) in the distributions were observed between the treatment arms at week 32. LS, least-squares. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43428/abstract.

groups were typically consistent with those in the overall population, which mostly consisted of patients with pcJIA, there were fluctuations of improvement that were largely driven by the small sample sizes of these two patient groups.

The observation that improvements at the end of part 1 with tofacitinib (week 18) were generally maintained at week 44 in the placebo group may suggest a prolonged biologic effect of tofacitinib on patient-reported and perceived impacts of JIA that persisted once treatment was switched to placebo. As previously reported, more patients receiving placebo discontinued during part 2 of the study compared with patients receiving tofacitinib (55% vs 31%, respectively), with the majority of patients discontinuing due to flares (52% vs 25%, respectively).[24] Analysis of long-term follow-up data could inform on whether any minimal deterioration in PROs reported due to flare may later be reversed.

The functional limitation and disability resulting from JIA can contribute to reduced HRQoL by restricting a patient's mobility and activities. Indeed, it has previously been observed that a CHAQ score of >1 is the strongest determinant of poorer HRQoL in CHQ PhS, indicating that functional impairment has a profound impact on physical well-being.[3] In the current study, CHAQ scores improved from baseline during part 1, and these improvements were generally maintained with scores between 0.5 to 0.6 wthrough to week 44, regardless of treatment arm. Furthermore, we observed substantial improvements in "physical function" and "role/social limitations–physical" CHQ health concepts; improvement in physical function may therefore be associated with improved physical well-being and allow patients greater mobility to resume their daily activities.

Consistent with previous studies in patients with JIA, CHQ PhS scores were considerably lower than CHQ PsS scores at baseline[4,5] and were approximately 2 SD below the standardized mean score of a normative population (mean 50 ± SD 10).[5] Substantial increases from baseline were observed in CHQ PhS scores, which reached the normative population values at week 18 and were generally maintained at week 44 in both the tofacitinib and the placebo groups. Although CHQ PsS scores demonstrated slight numerical improvement from baseline at week 18, which was generally maintained at week 44, mean scores were within normative population values throughout the study irrespective of treatment group. Notably, the differences in scores observed are unlikely to be clinically meaningful. Furthermore, the

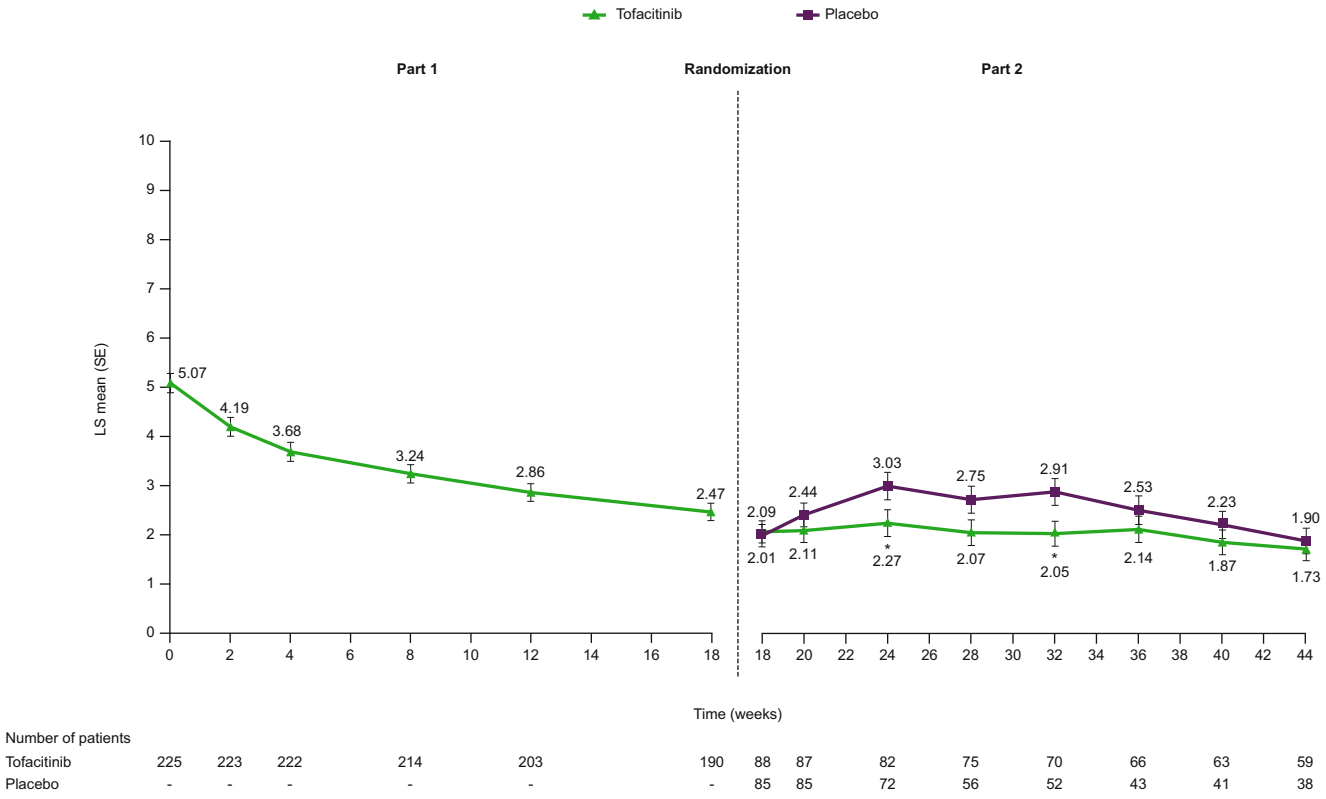

Figure 3. LS mean (±SE) patient overall well-being scores over time in patients with juvenile idiopathic arthritis treated with tofacitinib in part 1 and tofacitinib or placebo in part 2 (overall population). *$P < 0.05$ vs placebo. Analyses were based on observed data; missing values were not imputed. Dashed line represents randomization (patients meeting the juvenile idiopathic arthritis American College of Rheumatology 30 response criteria randomized 1:1 to continue tofacitinib or switch to placebo for up to an additional 26 weeks). Median and interquartile range values for patient overall well-being are summarized in Supplementary Table 3; no significant differences in the distributions were observed between the treatment arms during part 2. LS, least-squares. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43428/abstract.

patterns observed with treatment in both the CHQ PhS and PsS are consistent with those observed previously in patients with JIA treated with abatacept[5] or MTX.[4]

Duration of morning stiffness was substantially reduced during part 1 with tofacitinib treatment. Although there was a slight numerical increase in the duration of morning stiffness for both treatment arms in part 2, patients receiving placebo demonstrated numerically higher durations of stiffness throughout compared with patients receiving tofacitinib. This trend in improvement is generally similar to that observed in adults with rheumatoid arthritis who received 12 months of tofacitinib monotherapy, although adult patients demonstrated longer durations of morning stiffness versus the current population.[29]

The disease burden associated with JIA includes disability, joint pain, and reduced HRQoL, as previously reported by patients and their caregivers.[7,30,31] Indeed, pain has previously been identified as a core outcome by patients with JIA and their caregivers when evaluating the effects of treatments, highlighting it as an important outcome for those living with JIA.[15] Pain can contribute to impaired HRQoL; previous studies have observed that persistence of poor physical well-being following treatment with MTX was associated with several factors that included greater disability and pain[4] and that the intensity of a child's pain is a major predictor of poor psychosocial well-being.[3] Additionally, patients with JIA and higher levels of pain may experience more problems with their physical, emotional, and social functioning.[32] In the current analysis, tofacitinib improved arthritis pain during part 1, and these improvements were generally maintained at the end of part 2, regardless of treatment arm. Consistent with this observation, the CHQ health concept of "bodily pain" showed the largest improvement among the 15 CHQ health concepts at the end of part 1, with further, although more modest, improvement observed at the end of part 2 in patients receiving tofacitinib. The proportion of patients achieving minimal pain also generally increased during part 1 and was subsequently maintained in part 2 in patients receiving tofacitinib. Such improvements in pain may enable patients to resume day-to-day activities and, in school-age children, minimize time they are away from school, which can subsequently reduce stress placed on parents and/or caregivers.[33] Thus, alleviation of pain may contribute to a patient's improved physical, mental, emotional, and social functioning.

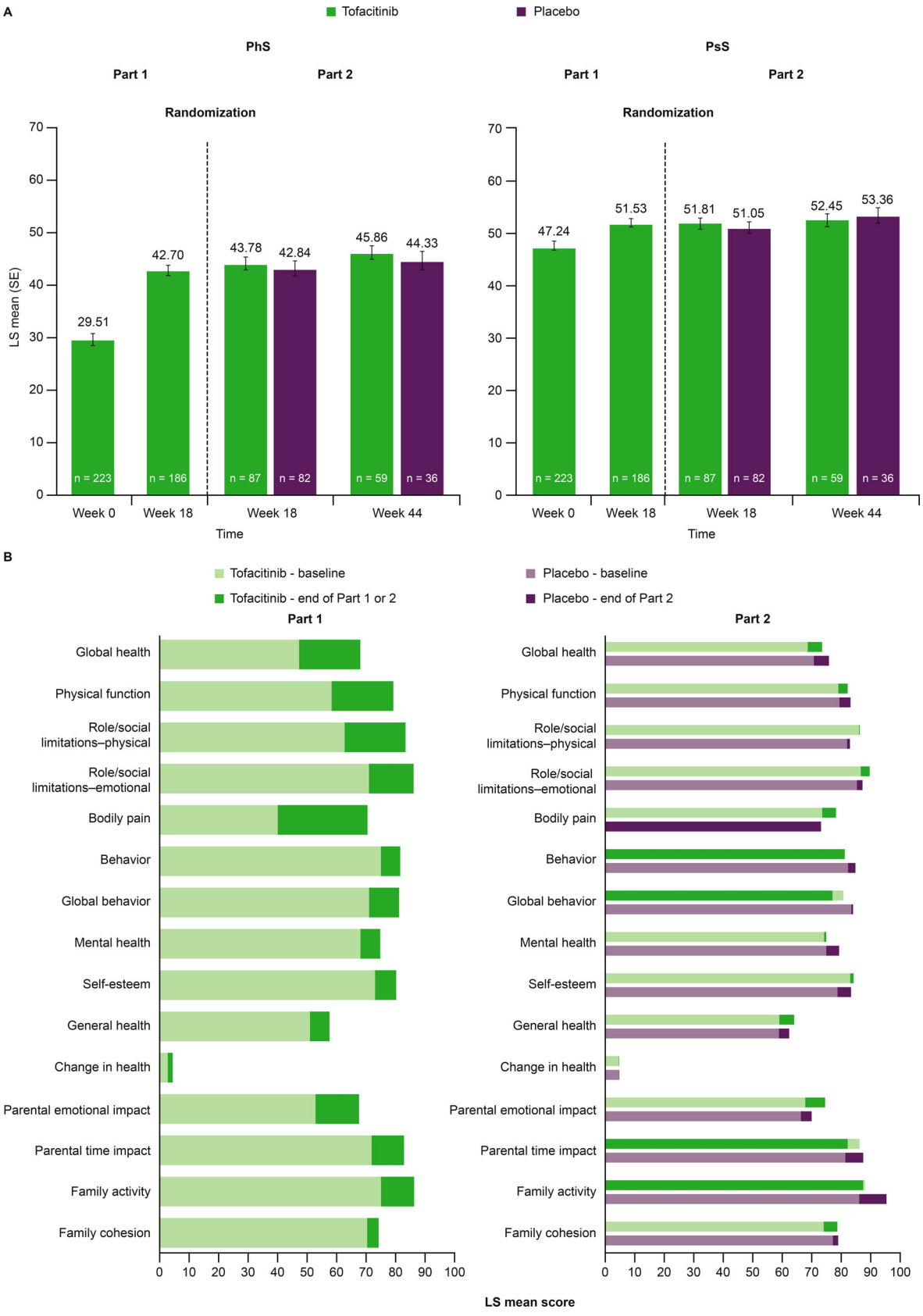

Figure 4. Legend on next page.

Figure 4. (A) LS mean (±SE) Child Health Questionnaire physical summary and Child Health Questionnaire psychosocial summary scores and (B) LS mean Child Health Questionnaire health concept scores at baseline and at the end of part 1 and part 2 in patients with juvenile idiopathic arthritis treated with tofacitinib in part 1 and tofacitinib or placebo in part 2 (overall population). Analyses were based on observed data; missing values were not imputed. Dashed line represents randomization (patients meeting the juvenile idiopathic arthritis American College of Rheumatology 30 response criteria randomized 1:1 to continue tofacitinib or switch to placebo for up to an additional 26 weeks). Median and interquartile range values for Child Health Questionnaire physical summary and psychosocial summary are summarized in Supplementary Table 3; no significant differences in the distributions between the treatment arms was observed during part 2. N values, medians, and interquartile range values for Child Health Questionnaire health concept scores are summarized in Supplementary Table 4. LS, least-squares; PhS, physical summary; PsS, psychosocial summary. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43428/abstract.

The effect of bDMARDs on pain, physical function, and HRQoL in patients with JIA has been investigated previously. Improvement in functional ability, pain, and well-being was observed over 104 weeks following biweekly intravenous infusion of tocilizumab in patients with sJIA or every 4 weeks for patients with pcJIA.[7] Furthermore, in a phase 3 withdrawal trial in pcJIA, substantial improvements in all CHQ health concepts, PhS, and PsS scores were observed during the four-month open-label period in patients receiving abatacept, with further improvements versus placebo in the six-month double-blind period.[5] Similar trends were observed for CHQ in a randomized trial with standard or higher doses of MTX in JIA.[4] Although comparisons between these studies and the current post hoc analysis are limited due to the different methodologies used, collectively, our observations highlight that tofacitinib, an oral treatment,[21,22] can improve HRQoL in patients with JIA, akin to other advanced therapies that are administered intravenously or subcutaneously.

There are a number of limitations to be considered when interpreting the findings of this analysis. The phase 3 study was powered for the analysis of the primary outcome, whereas the current analysis was post hoc in nature and therefore insufficiently powered for the assessment of additional outcomes. Because of the large number of outcomes assessed, the study findings should be interpreted with caution, given that correction for multiple testing was not performed. Although data for individual patient groups are provided in the Supplementary Materials, these data should be interpreted within the context of the reduced sample sizes, particularly for the jPsA or ERA groups. Additionally, per

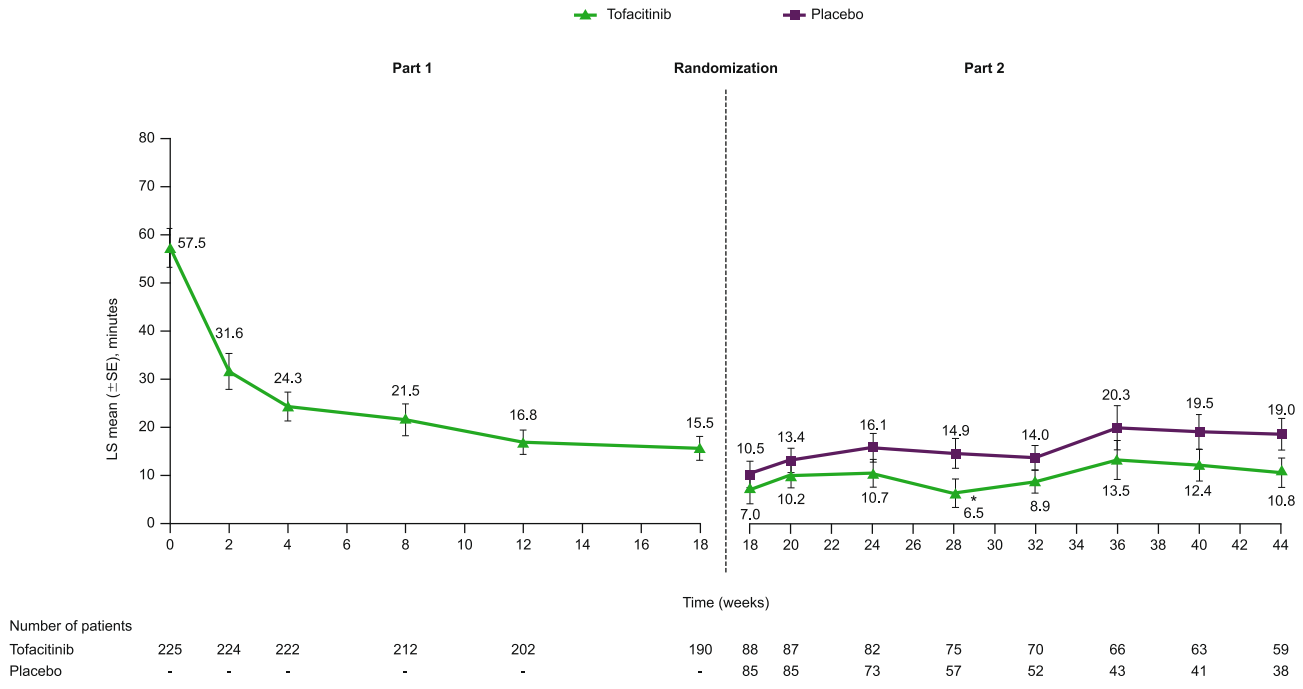

Figure 5. LS mean (±SE) duration of morning stiffness (minutes) in patients with juvenile idiopathic arthritis treated with tofacitinib in part 1 and tofacitinib or placebo in part 2 (overall population). *$P < 0.05$ vs placebo. Analyses were based on observed data; missing values were not imputed. Dashed line represents randomization (patients meeting the juvenile idiopathic arthritis American College of Rheumatology 30 response criteria randomized 1:1 to continue tofacitinib or switch to placebo for up to an additional 26 weeks). Median and interquartile range values for the duration of morning stiffness are summarized in Supplementary Table 3; significant differences ($P < 0.05$) in the distributions were observed between the treatment arms at weeks 28 and 40. LS, least-squares. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43428/abstract.

the trial protocol, the CHAQ assessments were administered to the patient's parent and/or legal guardian at each visit. Patients aged ≥14 years old could complete the assessment themselves; however, the responses used in the analysis were from the parent and/or legal guardian version of the CHAQ, rather than the patient version. Finally, the results may be influenced by the discontinuation of patients who experienced JIA flares, as per the trial protocol (data for these patients were not imputed for these post hoc analyses). It would be expected that JIA flare would be accompanied by worsening of PROs, which would not be captured at postdiscontinuation timepoints in our analyses. Patients who discontinued due to JIA flares could enter the LTE study (NCT01500551) and continue and/or reinitiate treatment with open-label tofacitinib. Although it was beyond the scope of this analysis to separately evaluate those patients who restarted tofacitinib in the LTE study, an interim analysis of the full LTE population found that improvements in CHAQ-DI scores, arthritis pain, and well-being were generally sustained through <48 months of open-label treatment with tofacitinib.[34]

In conclusion, among patients with pcJIA, jPsA, or ERA who had inadequate response to one or more DMARD, tofacitinib use was associated with sustained improvements in a range of PROs that encompassed disability and/or physical function, arthritis pain, well-being, and HRQoL up to approximately one year. These benefits were often maintained even in patients randomized to placebo in the double-blind phase of the study after receiving open-label tofacitinib in part 1. Collectively, our findings demonstrate that tofacitinib may provide substantial improvement in HRQoL for patients with JIA.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Brunner confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

This study was sponsored by Pfizer. The phase 3 trial was designed jointly by PRINTO/PRCSG investigators (NR, HIB, AM, and DJL) and the sponsor. Data were collected by the PRINTO/PRCSG investigators. The sponsor was involved in the overall management of the trial, data collection, and data analysis. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors and did not receive payment for development of this article. Authors from Pfizer were involved in the study design, data analysis, interpretation of data, and writing of the manuscript, and approved the content of the submitted manuscript. Medical writing support, under the direction of the authors, was provided by Robert Morgan, PhD, of CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer Inc, New York, NY, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (*Ann Intern Med* 2022;175:1298–1304). Pfizer was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. Publication of this article was not contingent upon approval by Pfizer.

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