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CLINICAL SCIENCE

Safety and efficacy of tofacitinib for the treatment of patients with juvenile idiopathic arthritis: preliminary results of an open-label, long-term extension study

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ABSTRACT

Objectives We report the safety, tolerability and efficacy of tofacitinib in patients with juvenile idiopathic arthritis (JIA) in an ongoing long-term extension (LTE) study.

Methods Patients (2–<18 years) with JIA who completed phase 1/3 index studies or discontinued for reasons excluding treatment-related serious adverse events (AEs) entered the LTE study and received tofacitinib 5 mg two times per day or equivalent weight-based doses. Safety outcomes included AEs, serious AEs and AEs of special interest. Efficacy outcomes included improvement since tofacitinib initiation per the JIA-American College of Rheumatology (ACR)70/90 criteria, JIA flare rate and disease activity measured by Juvenile Arthritis Disease Activity Score (JADAS)27, with inactive disease corresponding to JADAS ≤1.0.

Results Of 225 patients with JIA (median (range) duration of treatment, 41.6 (1–103) months), 201 (89.3%) had AEs; 34 (15.1%) had serious AEs. 10 patients developed serious infections; three had herpes zoster. Two patients newly developed uveitis. Among patients with polyarticular course JIA, JIA-ACR70/90 response rates were 60.0% (78 of 130) and 33.6% (47 of 140), respectively, at month 1, and generally improved over time. JIA flare events generally occurred in <5% of patients through to month 48. Observed mean (SE) JADAS27 was 22.0 (0.6) at baseline, 6.2 (0.7) at month 1 and 2.8 (0.5) at month 48, with inactive disease in 28.8% (36 of 125) of patients at month 1 and 46.8% (29 of 82) at month 48.

Conclusions In this interim analysis of LTE study data in patients with JIA, safety findings were consistent with the known profile of tofacitinib, and efficacy was maintained up to month 48.

Trial registration number NCT01500551.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tofacitinib is an oral Janus kinase inhibitor being investigated for several forms of juvenile idiopathic arthritis (JIA); it was approved by the US Food and Drug Administration in September 2020 for patients with polyarticular course JIA and by the European Medicines Agency in August 2021 for polyarticular JIA and juvenile psoriatic arthritis.

WHAT THIS STUDY ADDS

⇒ In this open-label, long-term extension (LTE) study, the safety profile of tofacitinib in patients with JIA was consistent with findings from the phase 3 JIA study.

⇒ No new safety findings were observed during 700 patient-years of follow-up that were unique to the JIA population treated with tofacitinib or new to the tofacitinib safety profile.

⇒ Clinical efficacy was maintained for at least 48 months of treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These interim results support the use of tofacitinib as an effective oral option for long-term use in patients with JIA. The final results of this LTE study will provide additional insight into the long-term benefit-to-risk profile of tofacitinib in patients with JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a group of chronic conditions leading to immune-mediated joint inflammation.[1] While there have been great improvements in long-term outcomes for patients with JIA in recent years, with the introduction of biological disease-modifying antirheumatic drugs (DMARDs),[2–9] at least one-third of patients respond poorly to treatment.[10–12]

Tofacitinib is an oral Janus kinase (JAK) inhibitor that was approved by the US Food and Drug Administration in September 2020 for the treatment of patients with polyarticular course (pc)

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JIA,[13] and by the European Medicines Agency in August 2021 for patients with polyarticular JIA or juvenile psoriatic arthritis (jPsA),[14] and is currently being investigated for systemic JIA.[15] A phase 1 study established the weight-based dosing regimen of tofacitinib tablets and oral solution for patients with JIA aged ≥2 years.[16] Subsequently, a 44-week randomised, double-blind, placebo-controlled, phase 3 withdrawal study in patients with pcJIA met its primary endpoint, in that tofacitinib-treated patients experienced a 54% reduction in flare risk compared with those receiving placebo.[17] In this clinical study, there was a rapid and profound improvement of disease, with achievement of JIA-American College of Rheumatology ≥30% improvement response (JIA-ACR30) occurring as early as week 2 and 77% of patients with pcJIA experiencing JIA-ACR30 by week 18 from commencing open-label tofacitinib. In addition, 26% of patients with pcJIA who continuously received tofacitinib treatment for 44 weeks achieved inactive disease status.

While double-blind, randomised controlled trials represent the gold-standard approach for determining the short-term efficacy and safety of therapies, long-term data are required to better understand the risk-to-benefit profile of a medication for the treatment of a chronic disease. Therefore, we conducted a long-term extension (LTE) study of patients with JIA who completed either of the phase 1 or phase 3 studies, or who discontinued for reasons excluding treatment-related serious adverse events (AEs). Here, we report the safety, tolerability and efficacy of tofacitinib in patients with JIA participating in the LTE study, with up to 105 months of observation.

METHODS

Study design

This ongoing LTE study is being conducted at centres of either the Paediatric Rheumatology INternational Trials Organisation (PRINTO, https://www.printo.it/)[18] or the Pediatric Rheumatology Collaborative Study Group (PRCSG, https://web.prcsg.org/)[19] in 22 countries. The study was designed to evaluate the long-term safety, tolerability and efficacy of tofacitinib in patients participating in the tofacitinib JIA programme, specifically the phase 1 pharmacokinetics study (NCT01513902[16]) and phase 3 placebo-controlled studies (NCT02592434[17]; NCT03000439 (ongoing)).

Patient visits occurred at baseline, month 1, month 3 and every 3 months thereafter while in the study. Uveitis assessment was performed on an annual basis. Written informed consent/assent was provided by parents/legal guardians/patients. The study is registered with ClinicalTrials.gov (NCT01500551).

Patients and treatment

Eligible patients were aged 2–<18 years and completed qualifying/index studies or discontinued the studies for reasons other than treatment-related serious AEs (patients who turned 18 years of age during the qualifying/index studies or who would turn 18 years of age during the LTE study were included). Key exclusion criteria included persistent oligoarthritis, undifferentiated JIA or history of any other rheumatic autoimmune disease besides Sjögren's syndrome. Therefore, patients assessed for this interim analysis of the LTE study had pcJIA (ie, extended oligoarthritis, rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis or systemic JIA (sJIA) without active systemic features), enthesitis-related arthritis (ERA) or jPsA.

All patients received open-label tofacitinib 5 mg two times per day or an equivalent weight-based lower dose (online supplemental table 1). Maximum dosages of allowable background JIA therapies included methotrexate (≤25 mg/week or ≤20 mg/m^2/week, whichever was lower), oral glucocorticoids (≤0.2 mg/kg/day or 10 mg/day of prednisone or equivalent, whichever was lower) and leflunomide (10 mg every other day, 10 mg/day or 20 mg/day, in patients weighing <20 kg, 20–40 kg or >40 kg, respectively). Dosages of background JIA therapy could be changed by the treating physician during the LTE study only.

Safety outcomes

Safety outcomes included AEs, serious AEs, permanent discontinuation due to AEs, temporary discontinuation due to AEs, AEs of special interest, laboratory test abnormalities and change from baseline in haemoglobin, lymphocytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol and creatine kinase. AEs were coded per the Medical Dictionary for Regulatory Activities (MedDRA), V.25.0, and reported by Preferred Terms.

AEs of special interest were deaths, active uveitis (newly diagnosed uveitis or worsening of existing uveitis),[20] serious infections, herpes zoster, tuberculosis and other opportunistic infections, gastrointestinal perforation, hepatic events, macrophage activation syndrome,[21] interstitial lung disease, malignancies excluding non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE), NMSC, thrombotic events and renal events. Safety event adjudication committees external to the study sponsor were established. Adjudication was carried out by committee members who were blinded to treatment assignment to allow for unbiased assessments. Additionally, an internal committee of medically qualified personnel employed by the study sponsor was established for adjudication of potential events of interstitial lung disease. An independent data safety monitoring board external to the study sponsor reviewed safety data on a cumulative basis.

Efficacy outcomes

Efficacy was assessed in patients with pcJIA, jPsA and ERA separately. Efficacy outcomes were assessed in patients with sJIA without active systemic features; however, due to low patient numbers, these data were not reported separately.

Efficacy evaluations considered the JIA core set variables,[22] which are physician's global evaluation of overall disease activity (0–10, with 0 indicating no disease activity), patient/parent assessment of overall well-being (0–10, with 0 indicating best well-being), number of joints with active arthritis, number of joints with limitation of motion and a laboratory measure of inflammation (C reactive protein (CRP) and erythrocyte sedimentation rate (ESR)). The Childhood Health Assessment Questionnaire–Disability Index (CHAQ-DI; 0–3, with higher scores indicating more disability) was assessed as a measure of physical function.[23 24] Values of the CHAQ-DI can be interpreted as the following levels of disability: 0, none; >0–0.24, mild; 0.25–0.71, mild to moderate; 0.72–1.53, moderate; and >1.53, more than moderate.[24] Patient/parent assessment of child's pain was also assessed (0–10, with 0 indicating no pain). Pain levels may be interpreted as follows: 1–4, mild; 5–6, moderate; and 7–10, severe.[25]

Disease control and JIA improvement over time were measured in several ways:

a. Juvenile Arthritis Disease Activity Score in 27 joints, based on CRP (JADAS; range: 0–57). In patients with pcJIA, jPsA or ERA with >4 active joints, JADAS disease activity level

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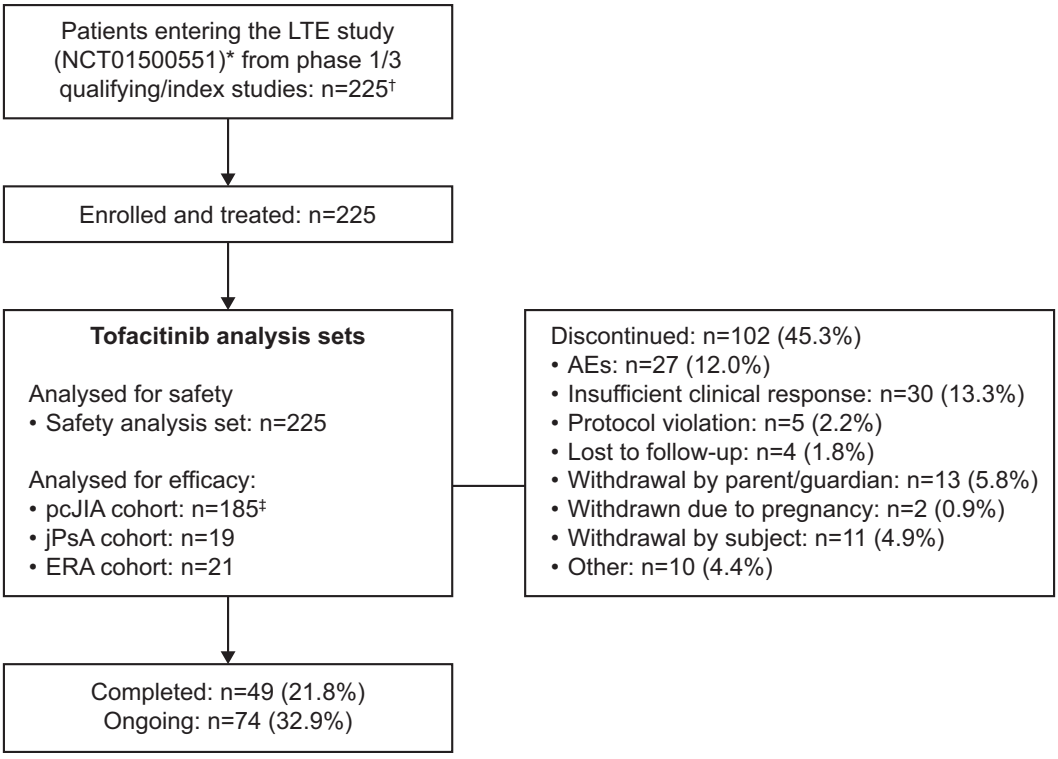


Figure 1 Patient disposition. *The data cut-off date was 11 July 2022. †Patients who entered the LTE study included 26 patients with either pcJIA, jPsA or ERA from a phase 1 qualifying/index study (NCT01513902), and 199 patients with either pcJIA, jPsA or ERA from a phase 3 qualifying/index study (NCT02592434). ‡The 185 patients with pcJIA were classified as follows: extended oligoarthritis, n=27; rheumatoid factor-positive polyarthritis, n=36; rheumatoid factor-negative polyarthritis, n=111; and systemic JIA without active systemic features, n=11. AEs, adverse events; ERA, enthesitis-related arthritis; jPsA, juvenile psoriatic arthritis; LTE, long-term extension; n, number of patients; pcJIA, polyarticular course juvenile idiopathic arthritis.

cut-offs were: high disease activity, scores >8.5; moderate disease activity, scores >3.8–≤8.5; low disease activity, scores >1.0–≤3.8; and inactive disease, scores ≤1.0. In patients with jPsA or ERA with ≤4 active joints, JADAS cut-offs were: high disease activity, scores >4.2; moderate disease activity, scores >2–≤4.2; low disease activity, scores >1–≤2.0; and inactive disease, scores ≤1.0.[26] JADAS minimal disease activity was assessed and defined as scores ≤3.8 in patients with pcJIA, and jPsA or ERA with >4 active joints; and as scores ≤2.0 in patients with jPsA or ERA with ≤4 active joints.[27]

b. Improvement from baseline as per the JIA-ACR criteria at the 30/50/70/90/100 response level, defined as ≥30/50/70/90/100% improvement from baseline in three of six JIA core set variables, with a worsening of ≥30% from baseline in ≤1 variable.[22] In patients with sJIA, absence of fever due to sJIA in the preceding 7 days was also required.
c. Flare events as per the PRCSG/PRINTO criteria, defined as a worsening of ≥30% in ≥3 of 6 JIA-ACR core set variables, with ≤1 variable improving by ≥30%, at each visit after month 3.[28] JIA-ACR core set variables at month 3 were used as baseline with evaluations starting at month 6.
d. JIA control as per the ACR provisional criteria of inactive disease (JIA-ACR-ID),[29] defined as absence of all of the following signs/symptoms attributable to JIA activity: active arthritis; fever, rash, serositis, splenomegaly, hepatomegaly or generalised lymphadenopathy; active uveitis; abnormal ESR or CRP levels and morning stiffness >15 min; plus a physician's global evaluation of overall disease activity as 'best possible' (assessed in this study as a score of 0 on a 21-circle Visual Analogue Scale, indicating no activity). JIA-ACR clinical remission (JIA-ACR-CR) was defined as JIA-ACR-ID for 6 months continuously while on medications.

Statistical analysis

The Consolidated Standards of Reporting Trials[30 31] and Strengthening the Reporting of Observational Studies in Epidemiology[32] statements were followed. In this interim analysis, up to 105 months of observation were available for analysis at the time of the data cut-off (11 July 2022; database not locked and data subject to change). However, due to the limited number of patients at later time points, efficacy analyses were reported up to month 48 only.

The safety analysis included all patients in the LTE study who received ≥1 dose of tofacitinib. Safety events were reported from LTE baseline through to data cut-off and were summarised descriptively. Changes from baseline in haemoglobin, lymphocyte count, AST, ALT and creatine kinase were reported at each visit up to month 87; change from baseline in cholesterol was reported up to month 84. Incidence rates (number of patients with first event per 100 patient-years of follow-up) were calculated for AEs of special interest. The risk period was defined as the time from the first dose of tofacitinib until the last dose of tofacitinib plus 28 days, last contact date or the data cut-off date, whichever came first.

Efficacy data were reported using observed data, without imputation, from patients receiving ≥1 dose of tofacitinib. Specifically, we calculated rates of JIA-ACR30/50/70/90/100 responses, JIA-ACR-ID and JIA-ACR-CR for the pcJIA cohort. JIA-ACR30/50/70/90/100 responses were also calculated for

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Table 1 Patient demographics and baseline* disease characteristics in the overall cohort

	Tofacitinib (N=225)
Female sex, n (%)	169 (75.1)
Age (years), mean (range)	12.2 (3–18)
Race: white,† n (%)	200 (88.9)
Duration of disease (years), mean (SD)	
pcJIA (n=185)	
Extended oligoarthritis (n=27)	4.7 (2.7)
RF-positive polyarthritis (n=36)	3.2 (2.4)
RF-negative polyarthritis (n=111)	4.6 (3.9)
sJIA without active systemic features (n=11)	5.3 (4.1)
jPsA (n=19)	3.2 (3.6)
ERA (n=21)	3.3 (2.3)
History of uveitis, n (%)	1 (0.4)
RF positive,‡ n (%)	36 (16.0)
ANA positive,§ n (%)	90 (40.0)
CRP (mg/dL),¶ median (Q1, Q3)	0.2 (0.0, 0.9)
JIA-ACR core set variables, median (Q1, Q3)	
Physician's global evaluation of overall disease activity	6.0 (4.5, 7.5)
Patient/parent assessment of overall well-being**	5.0 (3.0, 7.0)
Number of joints with active arthritis††	10.0 (7.0, 15.0)
Number of joints with limitation of motion	6.0 (3.0, 11.0)
CHAQ-DI**	0.9 (0.3, 1.5)
ESR (mm/hour)‡‡§§	16.0 (10.0, 32.0)
JADAS,** median (Q1, Q3)	19.5 (15.5, 26.0)
JADAS high disease activity,**¶¶ n (%)	201 (89.3)
JADAS moderate disease activity,**¶¶ n (%)	4 (1.8)
JADAS low disease activity,**¶¶ n (%)	1 (0.4)
JADAS-ID,**¶¶ n (%)	0 (0.0)
Duration of morning stiffness (min),§§ median (Q1, Q3)	30.0 (15.0, 60.0)
Patient/parent assessment of child's pain,** median (Q1, Q3)	5.8 (3.5, 7.0)
Prior medication use, n (%)	
Conventional synthetic DMARDs	199 (88.4)
Biological DMARDs	69 (30.7)
Concomitant medication use, n (%)	
Methotrexate	148 (65.8)
Corticosteroids	101 (44.9)
NSAIDs	173 (76.9)
Hormonal contraceptive	33 (14.7)
Vaccinated against VZV, n (%)	116 (51.6)

The overall cohort included all patients with pcJIA, jPsA or ERA.
*Baseline values were those from the qualifying/index study, except for patients with >14 days between the last visit of the qualifying/index study and enrolment into the LTE study, for whom baseline values were derived from the final pre-drug visit (ie, LTE baseline) on entry to the LTE study. Baseline values from the qualifying/index study were used for 216 patients (96.0%); baseline values from the LTE study were used for 9 patients (4.0%).
†Non-white patients included black, n=5 (2.2%) and other, n=20 (8.9%).
‡A total of 148 patients with pcJIA were evaluated for RF-positive or RF-negative status.
§A total of 215 patients were evaluated for ANA-positive or ANA-negative status.
¶For CRP, the normal range was 0–0.287 mg/dL.
**206 patients were evaluated for CHAQ and JADAS.
††Active arthritis defined as 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.
‡‡For ESR, the normal range was 0–20 mm/hour.
§§A total of 199 patients were evaluated for ESR and duration of morning stiffness.
¶¶In patients with pcJIA and jPsA or ERA with >4 active joints, JADAS disease activity level cut-offs were: high disease activity, scores >8.5; moderate disease activity, scores >3.8–≤8.5; low disease activity, scores >1.0–≤3.8; and inactive disease, scores ≤1.0. In patients with jPsA or ERA with ≤4 active joints, JADAS cut-offs were: high disease activity, scores >4.2; moderate disease activity, scores >2–≤4.2; low disease activity, scores >1–≤2.0; and inactive disease, scores ≤1.0.[26]
ACR, American College of Rheumatology; ANA, antinuclear antibody; CHAQ, Childhood Health Assessment Questionnaire; CHAQ-DI, Childhood Health Assessment Questionnaire–Disability Index; CRP, C reactive protein; DMARDs, disease-modifying antirheumatic drugs; ERA, enthesitis-related arthritis; ESR, erythrocyte sedimentation rate; ID, inactive disease; JADAS, Juvenile Arthritis Disease Activity Score in 27 joints, based on C reactive protein; JIA, juvenile idiopathic arthritis; jPsA, juvenile psoriatic arthritis; LTE, long-term extension; N, number of patients in overall cohort; n, number of patients with characteristic/condition; NSAIDs, non-steroidal anti-inflammatory drugs; pcJIA, polyarticular course juvenile idiopathic arthritis; Q1, 25th percentile; Q3, 75th percentile; RF, rheumatoid factor; sJIA, systemic juvenile idiopathic arthritis; VZV, varicella zoster virus.

the jPsA and ERA cohorts. The baseline values used to assess improvement over time were those from the qualifying/index study, except for patients with >14 days between the last visit of the qualifying/index study and enrolment into the LTE study, for whom baseline values were derived from the final pre-drug visit (ie, LTE baseline) on entry to the LTE study.

For the purpose of determining JIA-ACR-ID status at each visit, the last uveitis assessment result was carried forward up to the next non-missing uveitis assessment prior to study discontinuation.

Mean JADAS was calculated for the pcJIA cohort and the frequencies of patients achieving JADAS minimal disease activity and JADAS-ID over time were calculated for patients with pcJIA, jPsA and ERA. With respect to patient-reported outcomes, median CHAQ-DI, patient/parent assessment of child's pain and patient/parent assessment of overall well-being scores were calculated for the pcJIA cohort.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Patients

The first patient entered the LTE study on 18 March 2013. All 26 patients who participated in the phase 1 pharmacokinetics study and 199 of the 225 patients from the completed phase 3 study were enrolled and treated in the LTE study[17] (figure 1). Thus, this interim analysis included data for 225 patients. Patient demographics and baseline disease characteristics (from the qualifying/index study, or from the LTE baseline if there was >14 days between the last visit of the qualifying/index study and enrolment into the LTE study) are summarised in table 1. The duration of tofacitinib treatment prior to entry into the LTE study ranged from 5 days to 44 weeks. The mean (median; range) duration of follow-up in the LTE study was 37.3 (42.3; 1.0–103.6) months, with a total of 700 patient-years of follow-up. The mean total duration of tofacitinib treatment (median; range) in the LTE study was 36.7 (41.6; 1–103) months.

Safety

A summary of AEs is presented in table 2. During 700 patient-years of follow-up, there were 1213 reported AEs and 201 of 225 (89.3%) patients experienced ≥1 AE. The most common AEs were upper respiratory tract infection (48 patients (21.3%)), JIA exacerbation (28 patients (12.4%)) and nasopharyngitis (27 patients (12.0%)).

There were 39 serious AEs reported, and 34 of 225 (15.1%) patients experienced ≥1 serious AE. AEs led to permanent discontinuation from the study in 29 of 225 (12.9%) patients; 'interferon gamma release assay positive' (n=3) was the most common MedDRA Preferred Term contributing to study discontinuation, followed by 'arthritis', 'abortion spontaneous', 'condition aggravated', 'disease risk factor', 'herpes zoster', 'JIA exacerbation', 'pregnancy' and 'suicide attempt' (n=2 for each term). Additionally, 83 of 225 (36.9%) patients temporarily discontinued tofacitinib or had their dose reduced due to AEs; these AEs were mostly in the infections and infestations System Organ Class. Five patients temporarily discontinued tofacitinib due to laboratory test abnormalities (per protocol) which included leucopenia and neutropenia (n=1), increased

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Table 2 Summary of safety during the LTE study in the overall cohort treated with tofacitinib

	Overall cohort (N=225)*
Patients with AEs, n (%)	201 (89.3)
Total number of AEs	1213
Patients with SAEs, n (%)	34 (15.1)
Total number of SAEs	39†
Patients who permanently discontinued due to AEs, n (%)	29 (12.9)
Patients who temporarily discontinued or had dose reduced due to AEs, n (%)	83 (36.9)
Most common AEs (≥5% by MedDRA Preferred Term), n (%)	
Upper respiratory tract infection	48 (21.3)
JIA exacerbation	28 (12.4)
Nasopharyngitis	27 (12.0)
Arthralgia	22 (9.8)
Viral infection	22 (9.80)
Urinary tract infection	21 (9.3)
Headache	20 (8.9)
Fever	20 (8.9)
Cough	19 (8.4)
Vomiting	19 (8.4)
Abdominal pain	19 (8.4)
Sinusitis	17 (7.6)
Influenza	17 (7.6)
SARS-CoV-2 test positive	16 (7.1)
COVID-19	15 (6.7)
Oropharyngeal pain	15 (6.7)
Arthritis	14 (6.2)
Nausea	14 (6.2)
Disease progression	13 (5.8)
Pharyngitis	13 (5.8)
Bronchitis	12 (5.3)
Ear infection	12 (5.3)
AEs of special interest, n (%); IR‡ (95% CI)	
Deaths	0; 0.00 (0.00 to 0.53)
Active uveitis§	2 (0.9); —
Serious infections	10 (4.4); 1.44 (0.69 to 2.65)
Renal events	8 (3.6); 1.16 (0.50 to 2.29)
Herpes zoster (non-serious and serious)¶	4 (1.8); 0.58 (0.16 to 1.47)
Adjudicated opportunistic infections (excluding tuberculosis)**	2 (0.9); 0.29 (0.04 to 1.03)
Adjudicated tuberculosis	0; 0.00 (0.00 to 0.53)
Adjudicated gastrointestinal perforation	0; 0.00 (0.00 to 0.53)
Adjudicated hepatic events	0; 0.00 (0.00 to 0.53)
Adjudicated MAS††	0; 0.00 (0.00 to 15.72)
Adjudicated interstitial lung disease	0; 0.00 (0.00 to 0.53)
Adjudicated malignancies (excluding NMSC)	0; 0.00 (0.00 to 0.53)
Adjudicated NMSC	0; 0.00 (0.00 to 0.53)
Adjudicated MACE	0; 0.00 (0.00 to 0.53)
Adjudicated DVT	0; 0.00 (0.00 to 0.53)
Adjudicated PE	0; 0.00 (0.00 to 0.53)
ATE	0; 0.00 (0.00 to 0.53)
Laboratory test abnormalities, n (%)‡‡	
Haemoglobin <0.8× LLN	9 (4.0)
Lymphocytes	
<0.8× LLN	23 (10.2)
>1.2× ULN	3 (1.3)
AST >3.0× ULN	0
ALT >3.0× ULN	6 (2.7)
Cholesterol >1.3× ULN‡‡	5 (2.3)
Creatine kinase >2.0× ULN	28 (12.4)

The safety analysis set included all patients with pcJIA, jPsA or ERA.
Safety assessments were reported from LTE baseline through to data cut-off. AEs and SAEs were assessed up to 365 days after the last dose of tofacitinib. Laboratory abnormalities were recorded up until the patient stopped treatment or the lag time expired.
*Mean total duration of tofacitinib treatment (median; range) was 36.7 (41.6; 1–103) months.
†By MedDRA System Organ Class, these were: gastrointestinal disorders (n=4); general disorders and administration site conditions (n=3); hepatobiliary disorders (n=2); infections and infestations (n=10); injury, poisoning and procedural complications (n=1); musculoskeletal and connective tissue disorders (n=5); nervous system disorders (n=2); pregnancy, puerperium and perinatal conditions (n=2); psychiatric disorders (n=8); renal and urinary disorders (n=1); reproductive system and breast disorders (n=1); and skin and subcutaneous tissue disorders (n=1).
‡Number of patients with first event per 100 patient-years. For IRs, only patients with events during the risk period were included in the numerator. The risk period extended from the patient's first dose of tofacitinib until the date of last dose of tofacitinib plus 28 days, last contact date or data cut-off, whichever occurred first.
§One patient had active uveitis at month 12; one patient had uveitis at month 27.
¶Three patients with serious cases and one patient with a non-serious case.
**Two serious cases of herpes zoster were adjudicated as opportunistic infections.
††Applicable to patients with sJIA without active systemic features only (N=11).
‡‡Cholesterol was evaluated in 221 patients.
AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATE, arterial thromboembolism; DVT, deep vein thrombosis; ERA, enthesitis-related arthritis; IR, incidence rate (patients with events per 100 patient-years); JIA, juvenile idiopathic arthritis; jPsA, juvenile psoriatic arthritis; LLN, lower limit of normal; LTE, long-term extension; MACE, major adverse cardiovascular event(s); MAS, macrophage activation syndrome; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients with events; N, number of patients evaluated; NMSC, non-melanoma skin cancer; pcJIA, polyarticular course juvenile idiopathic arthritis; PE, pulmonary embolism; SAEs, serious adverse events; sJIA, systemic juvenile idiopathic arthritis; ULN, upper limit of normal.

blood creatine kinase, increased AST and hypokalaemia (n=1), increased ALT (n=1) and neutropenia (n=2).

Two patients (0.9%) newly developed uveitis; one patient with pcJIA aged >10 years developed uveitis (left eye) at month 12 of the LTE study, which was considered mild in severity and resolved after approximately 5 weeks following treatment with dexamethasone sodium phosphate eye drops (no changes to tofacitinib dosing), while another patient with pcJIA aged <10 years developed bilateral uveitis at month 27, which was also mild in severity and resolved after approximately 21 weeks with no treatment (no changes to tofacitinib dosing). 10 (4.4%) patients experienced serious infections; these were herpes zoster (n=3), abscess limb (n=1), COVID-19 (n=1), *Escherichia* pyelonephritis (n=1), infectious mononucleosis (n=1), influenza (n=1), molluscum contagiosum (n=1), rhinovirus infection (n=1) and urinary tract infection (n=1).

Four patients experienced herpes zoster infections in total, three of which were considered to be serious infections; two patients experienced severe, multidermatomal herpes zoster that was adjudicated as opportunistic (one patient aged ≥10 years was vaccinated against the varicella zoster virus; one patient aged <10 years had experienced varicella zoster prior to study start), and one patient (≥10 years of age) experienced herpes zoster that was moderate in severity and did not meet the criteria for an opportunistic infection (patient had experienced varicella

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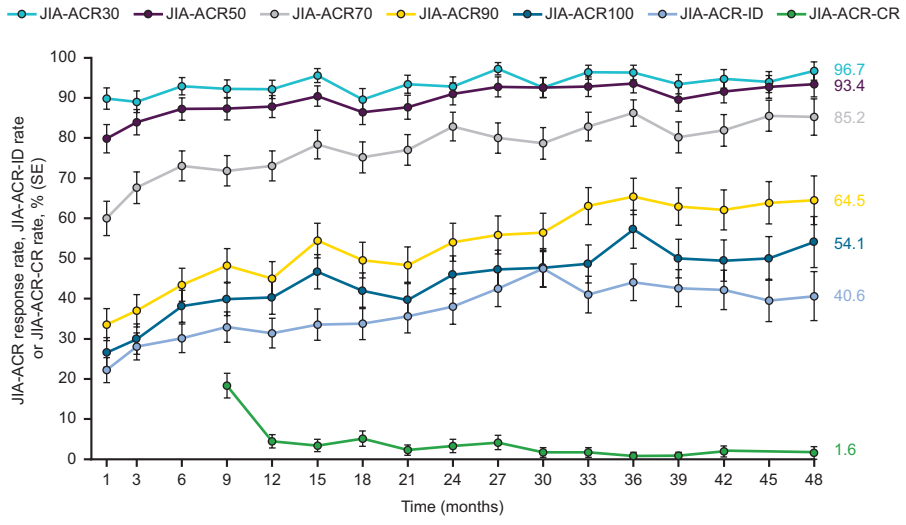
zoster prior to study start). One other patient (≥10 years of age) experienced herpes zoster that was determined to be non-serious, moderate in severity and did not meet the criteria for an opportunistic infection (the patient was vaccinated against the varicella zoster virus). All herpes zoster events resolved with treatment.

There were no deaths, and no reported cases of tuberculosis, gastrointestinal perforation, hepatic events, macrophage activation syndrome, interstitial lung disease, malignancies excluding NMSC, MACE, NMSC or thrombotic events. While there were no reported cases of tuberculosis, eight patients (3.6%) had a positive interferon gamma release assay, three of whom discontinued from the study (two aged ≥10 years and one aged <10 years).

Laboratory test abnormalities in haemoglobin, lymphocytes, AST, ALT, cholesterol and creatine kinase occurred in up to 12.4% of patients (table 2). During the LTE study, median haemoglobin, lymphocyte count, AST and ALT generally remained stable over time, with some fluctuations observed due to the low sample size at later time points (>month 60; online supplemental figure 1). Median cholesterol tended to increase over time, up to month 54. Creatine kinase increased from baseline at month 3 then remained relatively stable through to month 60 (online supplemental figure 1).

Efficacy

At month 1 of the LTE study, JIA-ACR30, JIA-ACR50, JIA-ACR70, JIA-ACR90 and JIA-ACR100 response rates in the pcJIA cohort were 89.8% (115 of 128), 79.8% (103 of 129), 60.0% (78 of 130), 33.6% (47 of 140) and 26.6% (38 of 143), respectively (figure 2); at month 48, these rates were 96.7% (59 of 61), 93.4% (57 of 61), 85.2% (52 of 61), 64.5% (40 of 62) and 54.1% (33 of 61), respectively. Of patients with pcJIA who reached the month 3 visit of the LTE, the JIA flare rate was generally <5% over the duration of the observation period (online supplemental figure 2). In patients with pcJIA who reached month 3 and had available data, 17.3% (28 of 162) experienced JIA flare by month 48 (online supplemental figure 3); similar rates of flare occurrence were observed in the jPsA and ERA groups.



JIA-ACR30, N	128	137	141	142	140	136	125	122	111	110	108	111	109	106	95	83	61
JIA-ACR50, N	129	137	141	142	140	136	125	122	111	110	108	111	109	106	95	83	61
JIA-ACR70, N	130	139	141	142	141	134	125	122	111	110	108	111	109	106	94	83	61
JIA-ACR90, N	140	146	145	143	140	134	125	120	111	111	108	111	110	108	95	83	62
JIA-ACR100, N	143	147	147	143	139	135	124	121	111	110	109	111	110	108	95	84	61
JIA-ACR-ID, N	180	178	166	158	156	146	136	132	121	120	118	117	118	115	102	86	64
JIA-ACR-CR, N	-	-	-	158	156	146	136	132	121	120	118	117	118	115	102	-	64

Figure 2 Efficacy in the pcJIA cohort up to month 48 (observed data): JIA-ACR30/50/70/90/100 response,* JIA-ACR-ID† and JIA-ACR-CR‡ rates. Baseline values for determining JIA-ACR30/50/70/90/100 response and JIA-ACR-ID rates were those of the qualifying/index study, except for patients with >14 days between the last visit of the qualifying/index study and enrolment into the LTE study, for whom baseline values were derived from the final pre-drug visit (ie, LTE baseline) on entry to the LTE study. Baseline values from the qualifying/index study were used for 177 (95.7%) patients with pcJIA; baseline values from the LTE study baseline were used for 8 (4.3%) patients with pcJIA. *The JIA-ACR30/50/70/90/100 response criteria were: ≥3 of 6 JIA core set variables improving by ≥30/50/70/90/100%, respectively, with ≤1 variable worsening by ≥30%.[22] In patients with sJIA, the absence of fever due to sJIA in the preceding 7 days was also required. †JIA-ACR-ID[29] was defined as absence of all of the following signs/symptoms attributable to JIA activity: active arthritis; fever, rash, serositis, splenomegaly, hepatomegaly or generalised lymphadenopathy; active uveitis; abnormal ESR or CRP levels, and morning stiffness of ≤15 min; plus a physician's global evaluation of overall disease activity as 'best possible' (assessed in this study as a score of 0 on a 21-numbered circle Visual Analogue Scale, indicating no activity). Uveitis assessment was imputed using last observation carried forward, prior to patient discontinuation. ‡Clinical remission was defined as JIA-ACR-ID for 6 months continuously while on medications. ACR, American College of Rheumatology; CR, clinical remission; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; ID, inactive disease; JIA, juvenile idiopathic arthritis; LTE, long-term extension; N, number of patients evaluated at each time point; pcJIA, polyarticular course juvenile idiopathic arthritis; sJIA, systemic juvenile idiopathic arthritis.

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At month 1 of the LTE, JIA-ACR response rates in patients with jPsA and ERA (online supplemental figure 4) were generally similar to those observed in patients with pcJIA. Response rates generally increased over time in patients with jPsA, though some variability was observed due the low sample size of this patient group.

In the pcJIA cohort, the JIA-ACR-ID rate was 22.2% (40 of 180) at month 1 and 40.6% (26 of 64) at month 48 among patients who remained in the study. The JIA-ACR-CR rate decreased from 18.4% (29 of 158) at month 9 to 1.6% (1 of 64) at month 48 (figure 2).

Observed mean (SE) JADAS in the pcJIA cohort was 22.0 (0.6) at baseline, 6.2 (0.7) at month 1 and 2.8 (0.5) at month 48 in patients who remained in the study (figure 3A). The JADAS-ID rate increased from baseline (0%) to 28.8% (36 of 125) at month 1 and 46.8% (29 of 62) at month 48 (figure 3B). In patients with jPsA, the JADAS-ID rate generally increased over time, while in patients with ERA, an increase from baseline in JADAS-ID rate was observed at month 1 with fluctuations in rate observed at later time points (online supplemental figure 5A,B).

In the pcJIA cohort, the JADAS minimal disease activity rate increased from baseline (0.6%; 1 of 169) to 52.0% (65 of 125)

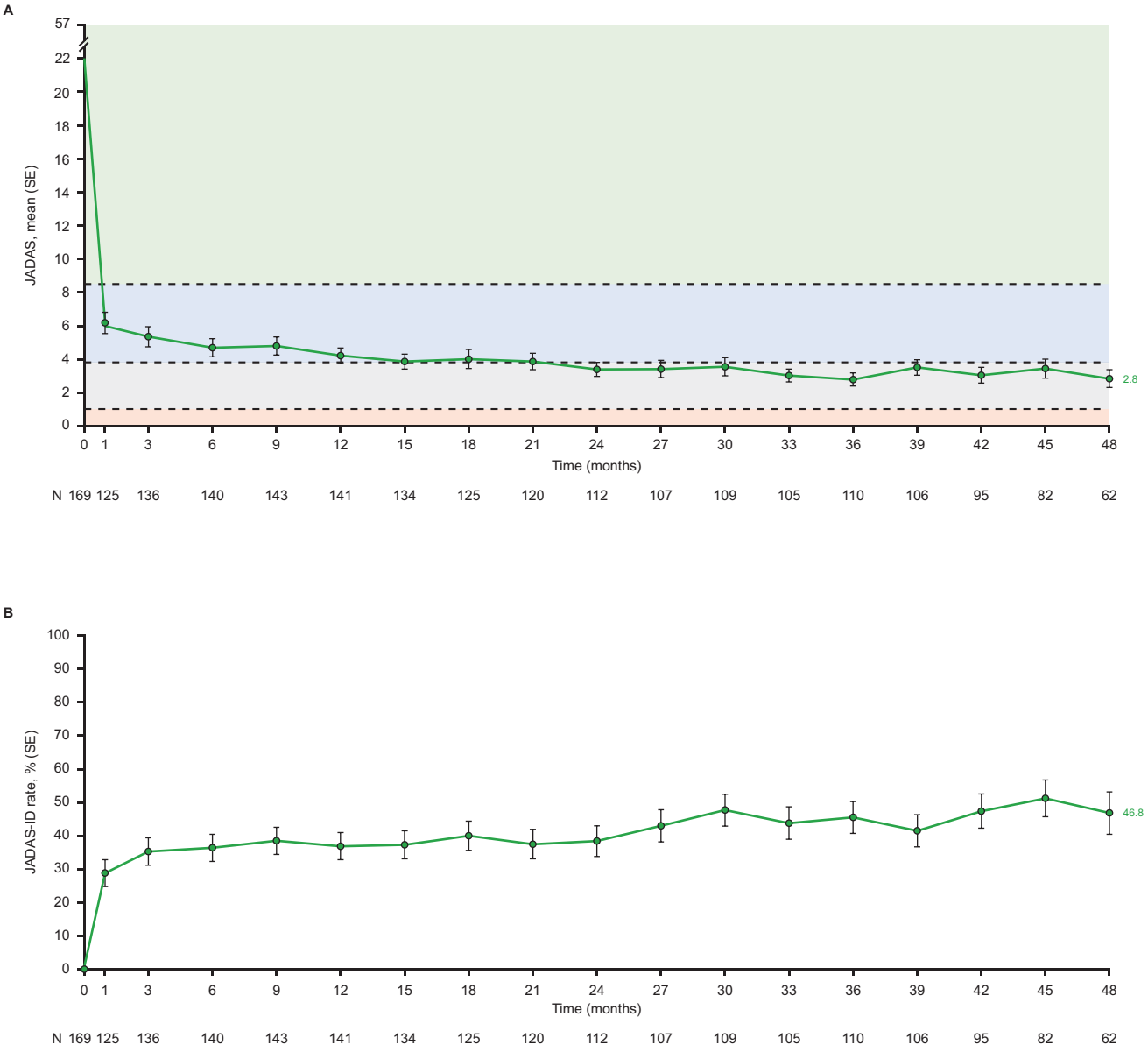


Figure 3 Efficacy in the pcJIA cohort up to month 48 (observed data): (A) mean JADAS* and (B) JADAS-ID rates. Baseline values were those of the qualifying/index study, except for patients with >14 days between the last visit of the qualifying/index study and enrolment into the LTE study, for whom baseline values were derived from the final pre-drug visit (ie, LTE baseline) on entry to the LTE study. Baseline values from the qualifying/index study were used for 177 (95.7%) patients with pcJIA; baseline values from the LTE study baseline were used for 8 (4.3%) patients with pcJIA. *Disease activity cut-offs are for patients with pcJIA, and jPsA or ERA with >4 active joints.[26] Shaded areas indicate the score thresholds for JADAS disease activity classifications: green, high disease activity (scores >8.5); blue, moderate disease activity (scores >3.8–≤8.5); grey, low disease activity (scores >1.0–≤3.8); and red, inactive disease (scores ≤1). Mean JADAS data with JADAS10 2021 disease activity cut-offs are provided in online supplemental figure 7. ERA, enthesitis-related arthritis; ID, inactive disease; JADAS, Juvenile Arthritis Disease Activity Score in 27 joints, based on C reactive protein; jPsA, juvenile psoriatic arthritis; LTE, long-term extension; N, number of evaluable patients; pcJIA, polyarticular course juvenile idiopathic arthritis.

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at month 1 and then continued to increase up to month 48 (online supplemental figure 6A). A similar trend was observed for patients with jPsA, while in patients with ERA, the JADAS minimal disease activity rate increased from baseline to month 1 and then fluctuated through to month 48 (online supplemental figure 6B,C).

There was sustained improvement in physical functioning; median (25th percentile, 75th percentile) CHAQ-DI score improved from 1.0 (0.3, 1.6) at baseline to 0.13 (0.0, 0.9) at month 1 and 0.0 (0.0, 0.6) at month 15 (figure 4A), and remained stable up to month 48. Improvements in patient/parent assessments of pain and overall well-being observed

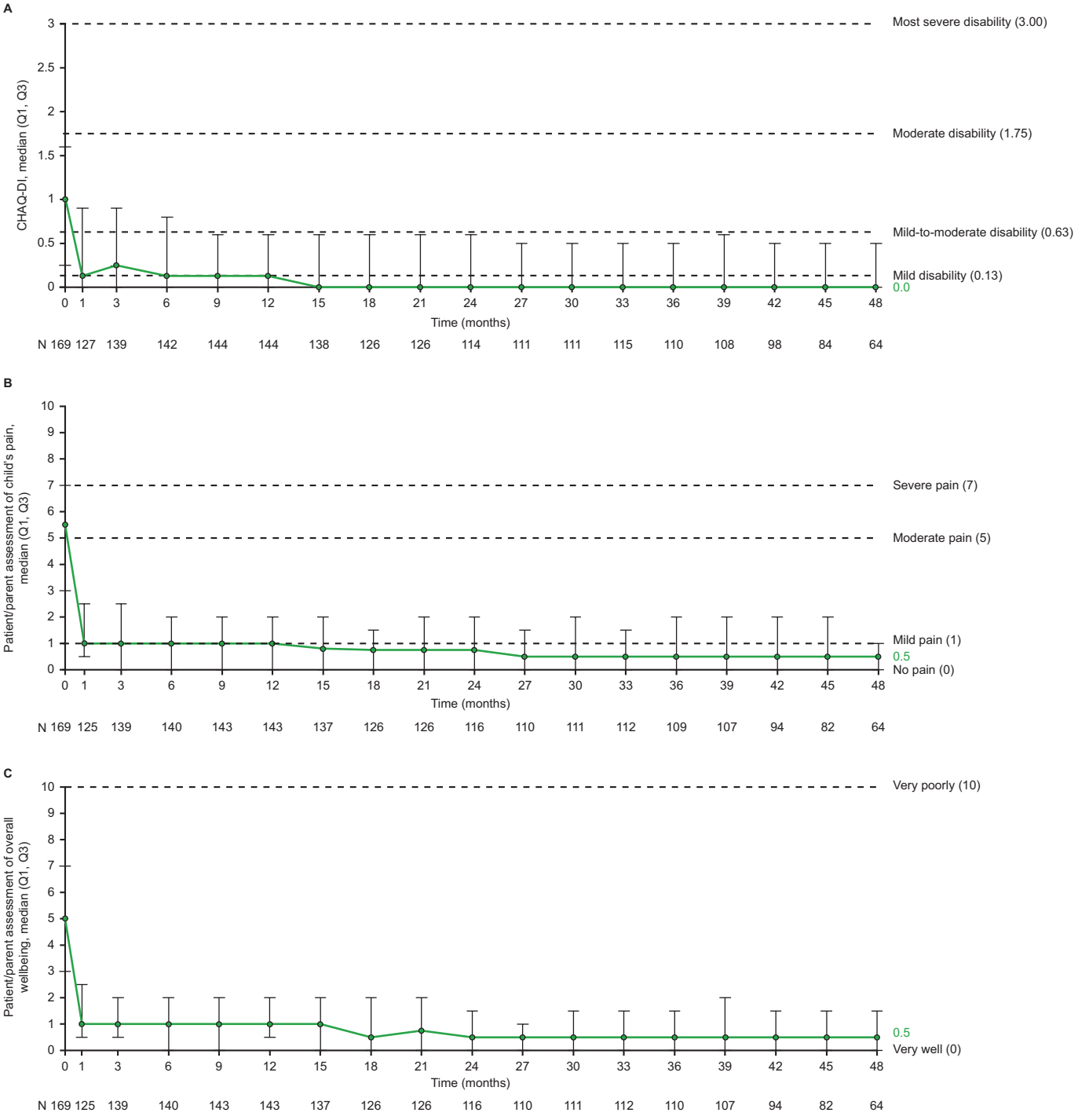


Figure 4 Efficacy in the pcJIA cohort up to month 48 (observed data): (A) median CHAQ-DI*; (B) median patient/parent assessment of child's pain†; and (C) median patient/parent assessment of overall well-being.† Baseline values were those of the qualifying/index study, except for patients with >14 days between the last visit of the qualifying/index study and enrolment into the LTE study, for whom baseline values were derived from the final pre-drug visit (ie, LTE baseline) on entry to the LTE study. Baseline values from the qualifying/index study were used for 177 (95.7%) patients with pcJIA; baseline values from the LTE study baseline were used for 8 (4.3%) patients with pcJIA. *The dotted lines in (A) (except for most severe disability) represent clinically meaningful median CHAQ-DI scores, which have been reported previously.[24] †The dotted lines in (B) represent interpretations of pain scores as reported previously.[25] CHAQ-DI, Childhood Health Assessment Questionnaire–Disability Index; LTE, long-term extension; N, number of evaluable patients; pcJIA, polyarticular course juvenile idiopathic arthritis; Q1, 25th percentile; Q3, 75th percentile.

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at month 1 were also generally sustained through month 48 (figure 4B,C).

DISCUSSION

This ongoing LTE study of patients with JIA treated with tofacitinib showed no new safety findings that were unique to the JIA population treated with tofacitinib or new to the tofacitinib safety profile during 700 patient-years of follow-up with up to 105 months of observation. Treatment responses observed at month 1 of the LTE study were generally consistent with those observed in patients receiving tofacitinib at the end of the phase 3 study and were generally maintained for at least 48 months.

The safety findings were generally consistent with those previously reported during the phase 3 JIA study.[17] Additionally, the safety profile observed in the current study was generally similar to that previously observed in patients with pcJIA receiving abatacept,[33] golimumab[34] or tocilizumab.[35] Serious infections and other AEs of special interest occurred in <5% of patients. While the disease courses of pcJIA, jPsA and ERA can be complicated by uveitis, it is reassuring that only 2 cases of uveitis were observed out of 225 patients in the LTE study. However, the effects of tofacitinib on the development or course of JIA-associated uveitis remain unclear.

Serious and opportunistic infections are more common in children with JIA versus those with chronic diseases not affecting the immune system,[36 37] with this difference in risk being particularly observed in young children.[38] In the current study, rates of serious and opportunistic infections in patients with JIA treated with tofacitinib appeared similar to those observed with the use of either glucocorticoids, methotrexate or tumour necrosis factor inhibitors.[36 37]

The use of JAK inhibitors, including tofacitinib, has been associated with herpes zoster events in adult patients with immune-mediated diseases such as rheumatoid arthritis, PsA and ulcerative colitis.[39–42] In the current study, herpes zoster infection did occur and appeared more frequent than what has been previously reported in JIA with biological DMARDs.[2–8] Herpes zoster events with tofacitinib occurred at an estimated mean rate of 0.58 per 100 patient-years of tofacitinib exposure in JIA. Notably, two of the four patients who experienced herpes zoster had been vaccinated against varicella zoster virus, while the other two patients had experienced varicella zoster prior to study start. This observation might prompt clinicians to carefully educate families regarding the risk of herpes zoster.

In ORAL Surveillance, cardiovascular risk-enriched adult patients with rheumatoid arthritis demonstrated a higher rate of MACE and cancers with tofacitinib, compared with tumour necrosis factor inhibitors[43]; risk differences of these outcomes were confined to patients who were ≥65 years of age, and/or long-time current/past smokers,[44] and those who had a history of atherosclerotic cardiovascular disease (MACE only).[45] While the current LTE study did not observe any cases of MACE or malignancies in a population of patients with JIA, and indeed, these differentiating risk factors are less applicable to the JIA population, the safety findings of ORAL Surveillance warrant a precautionary approach to apply these findings across all JAK inhibitors and all approved disease states, until data from additional dedicated safety studies (of sufficient size and duration) establish that this is not appropriate.

Current guidelines recommend treating JIA to the target of inactive disease, or at least to low or minimal disease activity.[46] Similar proportions of patients achieved inactive disease in the current LTE study, irrespective of the measure used; inactive disease was achieved by 22.2% and 28.8% of patients with pcJIA at month 1, and 40.6% and 46.8% of patients who remained in the study at month 48, as assessed by JIA-ACR-ID or JADAS-ID, respectively. It is important to emphasise that tofacitinib effectiveness was maintained over time, as supported by a low flare rate of generally <5% from months 6–48. Furthermore, physical functioning, as measured by CHAQ-DI, as well as patient/parent assessments of pain and well-being, showed sustained improvement over the duration of the follow-up, indicating that tofacitinib treatment improves patient/parent-reported outcomes in addition to those assessed by physicians. Specifically, in patients with pcJIA, median CHAQ-DI score reached 0 at month 15, which remained stable through month 48. Pain is one of the most important patient-reported outcomes for patients with JIA.[47] Tofacitinib treatment was also associated with marked improvement of pain as early as month 1 of the LTE study, with the median patient/parent assessment of child's pain decreasing from 5.50 at baseline to 1.00, which was sustained up to month 12 with further reductions in pain reported at later time points. Improvements in patient-reported outcomes have also been reported in patients with JIA after treatment with biological DMARDs, including tocilizumab and abatacept.[48 49]

There were some limitations to this analysis. This LTE study is ongoing, and the long-term safety and efficacy of tofacitinib in patients with JIA are yet to be determined. All analyses were descriptive, and no formal statistical analyses were carried out. In addition, determination of the impact of tofacitinib on safety outcomes was limited by the relatively small sample size, and the lack of a comparison to either placebo or active comparators. Data describing changes in the use of background medication prescribed for JIA (eg, corticosteroids) over the duration of the LTE study, such as additions, withdrawals and use of medication during flares, were not available, which is a significant limitation impacting interpretation of the efficacy findings. While a proportion of patients previously received placebo in the phase 3 index study (NCT02592434), these patients reinitiated tofacitinib on entering the LTE study. Therefore, the study population included patients who were continuing and reinitiating tofacitinib, with no stratification of these groups. Different baseline values were also used depending on the time between the last visit of the qualifying/index studies and enrolling in the LTE, which may have also affected the findings of this study. Additionally, the LTE study enrolled only patients from the qualifying/index studies, a population in whom the agent is known to be efficacious and well tolerated; therefore, the study population may not be representative of patients with JIA receiving tofacitinib in real-world settings. Furthermore, only a small number of patients in the study had jPsA and ERA, limiting interpretation of the results for these patient groups.

In conclusion, in this analysis of data from an ongoing LTE study, the safety and efficacy of tofacitinib in patients with JIA was at least maintained over time. Hence, tofacitinib appears to be an effective oral option for patients with JIA with an established safety profile. The final results of this LTE study will provide greater insight into the long-term benefit-to-risk profile of tofacitinib in patients with JIA, and will include an assessment of patients with sJIA with active systemic features.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the principles of the Declaration of Helsinki and applicable local regulatory requirements and laws. The study protocol was approved by the institutional review boards and/or independent ethics committee at each study centre. The protocol number (A3921145) was provided as the reference number. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. 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 de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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