Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial

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Summary

Background Tofacitinib is an oral Janus kinase inhibitor. This trial assessed the efficacy and safety of tofacitinib versus placebo in patients with polyarticular course juvenile idiopathic arthritis (JIA).

Methods This double-blind, withdrawal phase 3 trial enrolled patients with polyarticular course JIA (extended oligoarthritis, rheumatoid factor-positive or rheumatoid factor-negative polyarthritis, or systemic JIA without active systemic features) aged 2 years to younger than 18 years, and was done at 64 centres of the Paediatric Rheumatology International Trials Organisation and Pediatric Rheumatology Collaborative Study Group networks in 14 countries. Patients with psoriatic arthritis or enthesitis-related arthritis were enrolled for exploratory endpoints. During part 1 of the study, patients received oral open-label tofacitinib (weight-based doses; 5 mg twice daily or lower) for 18 weeks. Patients achieving at least JIA/American College of Rheumatology 30 response were randomly assigned (1:1) using an Interactive Response Technology system to continue tofacitinib or switch to placebo in part 2 of the study for 26 weeks. The primary endpoint was JIA flare rate by week 44 in part 2 in patients with polyarticular course JIA; the intention-to-treat principle was applied. Safety was evaluated throughout part 1 and part 2 of the study in all patients who received one dose or more of study medication. This trial is registered with ClinicalTrials.gov, NCT02592434.

Findings Between June 10, 2016, and May 16, 2019, of 225 patients enrolled, 184 (82%) patients had polyarticular course JIA, 20 (9%) had psoriatic arthritis, and 21 (9%) had enthesitis-related arthritis. 147 (65%) of 225 patients received concomitant methotrexate. In part 2, 142 patients with polyarticular course JIA were assigned to tofacitinib (n=72) or placebo (n=70). Flare rate by week 44 was significantly lower with tofacitinib (21 [29%] of 72 patients) than with placebo (37 [53%] of 70 patients; hazard ratio 0·46, 95% CI 0·27–0·79; p=0·0031). In part 2 of the study, adverse events occurred in 68 (77%) of 88 patients receiving tofacitinib and 63 (74%) of 85 in the placebo group. Serious adverse events occurred in one (1%) and two (2%), respectively. In the entire tofacitinib exposure period, 107 (48%) of 225 patients had infections or infestations. There were no deaths during this study.

Interpretation The results of this pivotal trial show that tofacitinib is an effective treatment in patients with polyarticular course JIA. New oral therapies are particularly relevant for children and adolescents, who might prefer to avoid injections.

Funding Pfizer.

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic conditions of unknown cause with onset occurring before the age of 16 years.[1]

Per current recommendations,[2–4] patients with the most severe forms, polyarticular course JIA and systemic JIA, are treated with conventional synthetic and biological disease-modifying antirheumatic drugs (DMARDs), which have considerably improved long-term outcomes over the past 30 years.[5–12] Despite therapeutic advances, many patients have an inadequate response.[12] In a US population-based cohort and a large North American registry, 45–52% of patients with JIA had active disease despite using two or more sequential biological DMARDs.[13] In an international study of more than 9000 patients with JIA who were seen consecutively for a period of 6 months, although 21–46% used biological DMARDs (varying by geographical region), 33–56% had active arthritis at last visit.[14]

Tofacitinib is an oral Janus kinase (JAK) inhibitor that is being investigated for several forms of JIA, and was first approved by the US Food and Drug Administration in September, 2020, for patients with polyarticular course JIA; in August, 2021, the European Commission approved it for patients with polyarticular JIA or juvenile psoriatic arthritis. Whereas biological DMARDs target

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Research in context

Evidence before this study

We searched PubMed (with no date restrictions) on Nov 25, 2020, for English language publications reporting clinical trials of Janus kinase inhibitors, including tofacitinib, in patients with juvenile idiopathic arthritis (JIA). The search used the terms (("tofacitinib" [All Fields] OR "Janus kinase inhibitor" [All Fields] OR "JAK inhibitor" [All Fields] OR "baricitinib" [All Fields] OR "filgotinib" [All Fields] OR "upadacitinib" [All Fields]) AND ("juvenile idiopathic arthritis" [All Fields] OR "JIA" [All Fields] OR "juvenile idiopathic arthritis" [MeSH Terms]) AND (Clinical Trial [Publication Type])). The search yielded only one result, which was the phase 1 open-label clinical trial (NCT01513902) that established dosing of tofacitinib tablets and oral solution in patients with JIA aged 2 years or older.

Added value of this study

This is the first phase 3 clinical trial assessing the efficacy and safety of a Janus kinase inhibitor in patients with JIA. JIA flare rate by week 44 (primary endpoint) was significantly lower with tofacitinib than with placebo in patients with polyarticular course JIA. These findings were supported by improvements with tofacitinib versus placebo in secondary efficacy endpoints relating to disease activity and physical functioning. Overall, the safety profile of tofacitinib in patients with JIA was consistent with the established safety profile of tofacitinib in adults with rheumatoid arthritis.

Implications of all the available evidence

The results of this pivotal phase 3 clinical trial suggest a favourable benefit–risk balance in patients with polyarticular course JIA treated with oral tofacitinib. Currently, conventional synthetic and biological disease-modifying antirheumatic drugs are recommended treatments for patients with polyarticular course JIA. However, many patients have an inadequate response to these treatments. Additional treatment options are, therefore, important, and oral therapies are particularly relevant for children and adolescents who might prefer to avoid injections.

extracellular elements of the inflammation pathway, JAK inhibitors target intracellular elements.[15] The efficacy and safety of tofacitinib tablets have been shown in adults with rheumatoid arthritis,[16] psoriatic arthritis,[17] and ulcerative colitis.[18] A phase 1 trial established dosing of tofacitinib tablets and oral solution in patients with JIA aged 2 years or older.[19]

The objective of this phase 3 trial was to assess the efficacy and safety of oral tofacitinib versus placebo in patients with polyarticular course JIA.

Methods

Study design and participants

This phase 3, two-part, randomised, double-blind, placebo-controlled withdrawal trial (appendix p 6) was done at 64 centres of the Paediatric Rheumatology International Trials Organisation (PRINTO) and Pediatric Rheumatology Collaborative Study Group (PRCSG) in 14 countries (Argentina, Australia, Belgium, Brazil, Canada, Israel, Mexico, Poland, Russia, Spain, Turkey, Ukraine, the UK, and the USA).

In the open-label, run-in phase (part 1; weeks 0–18), patients received tofacitinib for 18 weeks or until JIA flare. After 18 weeks, patients with a JIA/American College of Rheumatology (ACR) response of 30 or more were randomly assigned to continue tofacitinib or switch to placebo for 26 weeks, or until JIA flare, during the double-blind phase (part 2; weeks 18–44). Following this trial, patients could receive tofacitinib in a long-term extension study (NCT01500551).

Eligible patients were aged 2 to less than 18 years old and had one of the following forms of JIA per International League of Associations for Rheumatology classification criteria:[1] extended oligoarthritis, rheumatoid factor-positive or rheumatoid factor-negative polyarthritis, systemic JIA without systemic features for 6 months pre-enrolment, psoriatic arthritis, or enthesitis-related arthritis.

Patients with extended oligoarthritis, rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis, or systemic JIA without systemic features, collectively termed polyarticular course JIA, were required to have active disease defined as five or more active joints at enrolment, and an inadequate response to one or more DMARDs (methotrexate or biological DMARDs).

Patients with psoriatic arthritis or enthesitis-related arthritis were required to have active disease defined as three or more active joints at enrolment, and an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs). These patients were enrolled for a preliminary, exploratory assessment of tofacitinib in these JIA categories.

Patients with the following forms of JIA were excluded from the trial: systemic JIA with active systemic features other than active joints and elevated acute-phase reactants within 6 months of enrolment, persistent oligoarthritis, and undifferentiated JIA. Patients with active uveitis (according to Standardization of Uveitis Nomenclature criteria) within 3 months of enrolment were also excluded.

The trial was done in accordance with the Guidelines for Good Clinical Practice, 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. The protocol, which includes full inclusion and exclusion criteria and a

summary of protocol amendments, and the statistical analysis plan are provided in the appendix.

Randomisation and masking

Patients eligible to enter part 2 of the trial were randomly assigned (1:1) to continue tofacitinib or switch to placebo. Randomisation was stratified by JIA category (extended oligoarthritis, rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis, systemic JIA without active systemic features, psoriatic arthritis, or enthesitis-related arthritis), and baseline C-reactive protein (CRP) (normal versus elevated) in patients with polyarticular course JIA, to ensure a better representation of the population currently observed in clinical practice. Part 2 was masked to the patients, investigators, and sponsor. Allocation of patients to treatment groups was done using an Interactive Response Technology (IRT) system. The site personnel (study coordinator or specified designee) were required to enter or select information including, but not limited to, the user's identification and password, the protocol number, the patient number, and the patient's date of birth. The site personnel were then provided with a treatment assignment and dispensable unit or container number when drug was being supplied via the IRT system.

Procedures

Patients weighing 40 kg or more received 5 mg twice daily oral tofacitinib. Doses of tofacitinib for patients weighing less than 40 kg were selected to match the predicted steady-state average drug plasma concentrations in patients weighing 40 kg or more after receiving 5 mg twice daily,[19] as follows: 2 mg twice daily dose for 5 to less than 7 kg bodyweight; 2·5 mg twice daily dose for 7 to less than 10 kg bodyweight; 3 mg twice daily dose for 10 to less than 15 kg bodyweight; 3·5 mg twice daily dose for 15 to less than 25 kg bodyweight; and 4 mg twice daily dose for 25 to less than 40 kg bodyweight. Two treatment formulations were available: 5 mg tablet and 1 mg/mL grape-flavoured oral solution. Patients weighing 40 kg or more received 5 mg tablets, or 5 mL oral solution (1 mg/mL) if unable to swallow tablets. Patients weighing less than 40 kg received oral solution (1 mg/mL).

Tofacitinib tablets, oral solution, and matching placebo for oral administration were supplied in child-resistant bottles to the investigative sites by the sponsor. The treatment, along with written dosing instructions, and oral dosing syringes where appropriate, were dispensed by a qualified member of the study staff (eg physician, nurse, physician's assistant, practitioner, or pharmacist) to the parent, legal guardian, or patient, as allowed by local, state, and institutional guidance.

Patients could continue the following stable background therapies: NSAIDs; methotrexate (≤25 mg per week or ≤20 mg/m² per week, whichever was lower); and oral glucocorticoids (≤0·2 mg/kg per day of prednisone equivalent or ≤10 mg per day, whichever was lower). Intra-articular glucocorticoids could be administered in a total dosage of 2 mg/kg or less (up to 80 mg) of methylprednisolone equivalent every 6 months. No more than two joints could be injected in any given 6-month period and individual joints could not be injected more frequently than once in a 6-month period. Injected joints were considered active joints in efficacy assessments for the remainder of the study.

Study visits were scheduled at baseline, and at weeks 2, 4, 8, 12, 18, 20, 24, 28, 32, 36, 40, and 44 (appendix pp 43–46). Efficacy assessments, including the six validated JIA/ACR core set variables,[20] were done at each study visit by health-care professionals trained in the assessments. Safety assessments (adverse events and laboratory tests [including haematology and chemistry]) were done by a health-care professional at each study visit, except lipids were assessed only at baseline and weeks 4, 18, and 44, or discontinuation.

Disease activity was evaluated at each planned visit using the six validated JIA/ACR core set variables: physician's global evaluation of overall disease activity; patient or parent assessment of overall wellbeing; number of joints with active arthritis; number of joints with limitation of motion; validated translation of Childhood Health Assessment Questionnaire–Disability Index (CHAQ-DI);[21] and erythrocyte sedimentation rate. Response was assessed using the JIA/ACR response criteria. The JIA/ACR30/50/70/90/100 response criteria require: three of six JIA core set variables improving by at least 30%, 50%, 70%, 90%, and 100%, respectively, with no more than one of the remaining variables worsening by 30% or more.[20] In patients with systemic JIA, the absence of spiking fever related to systemic JIA was also required.

The following efficacy assessments were assessed and confirmed in real time, according to validated criteria, by independent evaluators at the PRINTO or PRCSG centralised coordinating centres: JIA core set variables[20,21] by certified joint assessors; JIA/ACR30/50/70/90/100 response;[20] JIA flare;[22] JIA/ACR inactive disease and clinical remission; and Juvenile Arthritis Disease Activity Score (JADAS) status.[23,24] Except for JIA flare and JIA/ACR-inactive disease status, which were obtained from the centralised coordinating centres database, all other efficacy endpoints reported here were calculated by Pfizer from the Case Report Form data.

Outcomes

All study outcomes are listed in the study protocol, which is provided in the appendix. Here, we describe endpoints reported in this Article. The primary endpoint was evaluated in part 2 of the study and secondary endpoints in both parts 1 and 2 of the study.

The primary endpoint was JIA flare rate by week 44 in part 2 of the study in patients with polyarticular course JIA. Flare was defined per PRCSG and PRINTO JIA flare criteria as a worsening of 30% or more in three or more

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of six JIA/ACR core set variables, with one or none of the variables improving by 30% or more.[22]

Key secondary efficacy endpoints in patients with polyarticular course JIA were: JIA/ACR30, JIA/ACR50, and JIA/ACR70 response rates[20] and mean change from part 2 baseline in CHAQ-DI score, all at week 44.

Other secondary efficacy endpoints included: time to JIA flare in part 2; JIA/ACR30, JIA/ACR50, JIA/ACR70, JIA/ACR90, and JIA/ACR100 response and JIA/ACR inactive disease rates[23] (ie, no joints with active arthritis; no fever, rash, serositis, splenomegaly, hepatomegaly, or generalised lymphadenopathy attributable to systemic JIA; no active uveitis; normal erythrocyte sedimentation rate or, if elevated, not attributable to JIA; physician global assessment of disease activity score of best possible; or duration of morning stiffness ≤15 min) over time in parts 1 and 2; achievement of JIA/ACR clinical remission[23] (inactive disease for 6 continuous months) at least once during part 2; mean values for JIA/ACR core set variables over time in parts 1 and 2; JADAS in 27 joints, based on CRP, over time in parts 1 and 2 (with disease activity level cutoffs overlaid); and JADAS minimum disease activity and JADAS inactive disease rates over time in parts 1 and 2. JADAS disease activity level cutoffs were: JADAS high disease activity (scores >8·5); JADAS moderate disease activity (scores 3·9–8·5); JADAS minimum disease activity (scores ≤3·8); JADAS low disease activity (scores 1·1–3·8); and JADAS inactive disease (scores ≤1).[25,26]

In patients with psoriatic arthritis or enthesitis-related arthritis, JIA flare rate by week 44 and mean JADAS over time in parts 1 and 2 were evaluated in prespecified exploratory analyses.

Safety endpoints included: adverse events coded using Medical Dictionary for Regulatory Activities version 22.0, adverse events of special interest, clinical laboratory abnormalities, and laboratory values over time (median and median change from baseline). These endpoints were assessed in part 1, part 2, and during the entire tofacitinib exposure period.

Statistical analysis

A sample size of approximately 170 patients (in the polyarticular course JIA cohort) was enrolled in the open-label active treatment run-in phase (part 1) to provide a power of approximately 90% or above to detect a difference in the rate of JIA flares between tofacitinib versus placebo in the double-blind phase (part 2), assuming a 54–65% JIA/ACR30 response rate from part 1, a two-sided 5% type 1 error, and a true difference of at least 31% in flare rates between tofacitinib and placebo, with a placebo flare rate of 57%. Sample sizes for the polyarticular course JIA categories were determined from a combination of prevalence data and precedents in the literature.

The intention-to-treat principle was applied for efficacy analyses (ie, efficacy data of all patients were analysed per randomised treatment group). The primary and key secondary efficacy analyses in part 2 were done in patients with polyarticular course JIA. Patients with psoriatic arthritis or enthesitis-related arthritis were excluded from the primary and key secondary efficacy analyses, but included in exploratory efficacy analyses and in the safety analysis. Safety was analysed in all patients who received at least one dose of study medication; patients were reported under the treatment that they received.

To control for type 1 error, JIA flare rate, JIA/ACR30/50/70 response rates, and mean change in CHAQ-DI score from baseline at week 44 were tested using a gate-keeping sequential approach. Superiority of tofacitinib over placebo was tested at a two-sided 0·05 significance level. For remaining analyses, nominal p values and 95% CIs are reported.

Upon discontinuation (except while in clinical remission), patients were considered to have JIA flare (part 2), and to not meet criteria for JIA/ACR30 response or better (parts 1 and 2), JIA/ACR inactive disease (parts 1 and 2), or JADAS minimum disease activity or JADAS-inactive disease (part 2), at all subsequent visits within part 1 or 2.

Binary endpoints, including the primary endpoint, were analysed using the normal approximation approach for binomial populations. JIA flare was measured relative to previous visit in part 1, and relative to randomisation visit in part 2. JIA/ACR response rates were calculated relative to part 1 baseline. Secondary continuous endpoints were analysed using a mixed-effect model with repeated measures, without imputation for missing data. Time to JIA flare analyses were done with the Kaplan-Meier method and the log-rank test.

A sensitivity analysis of the primary endpoint was performed using the Cochran-Mantel-Haenszel test with JIA category and baseline CRP (normal or elevated) as stratification factors.

For the primary endpoint of JIA flare rate by week 44 in part 2 and the type 1 error-controlled key secondary endpoint of JIA/ACR30 response at week 44, prespecified subgroup analyses were done using the following subgroups: JIA category (extended oligoarthritis, rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis, systemic JIA without active systemic features); part 1 baseline CRP (normal, elevated); age (2 to <6 years, 6 to <12 years, 12 to <18 years); geographical region (North America, South and central America, Europe, all other); and part 1 baseline bodyweight (<40 kg, ≥40 kg).

In part 2 and the entire tofacitinib exposure period, incidence rates (patients with events per 100 patient-years) were calculated for adverse events, serious adverse events, permanent discontinuations due to adverse events, and adverse events of special interest. An independent Data Safety Monitoring Board was responsible for ongoing monitoring of the safety of patients in the study.

All statistical analyses were done using SAS, version 9.4. The trial is registered with ClinicalTrials.gov, NCT02592434.

Role of the funding source
The study was sponsored by Pfizer. The 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. Under the supervision of the PRINTO and PRCSG officers, the first draft of the manuscript was written by an employee of CMC Connect, funded by Pfizer. Subsequent drafts were revised by the

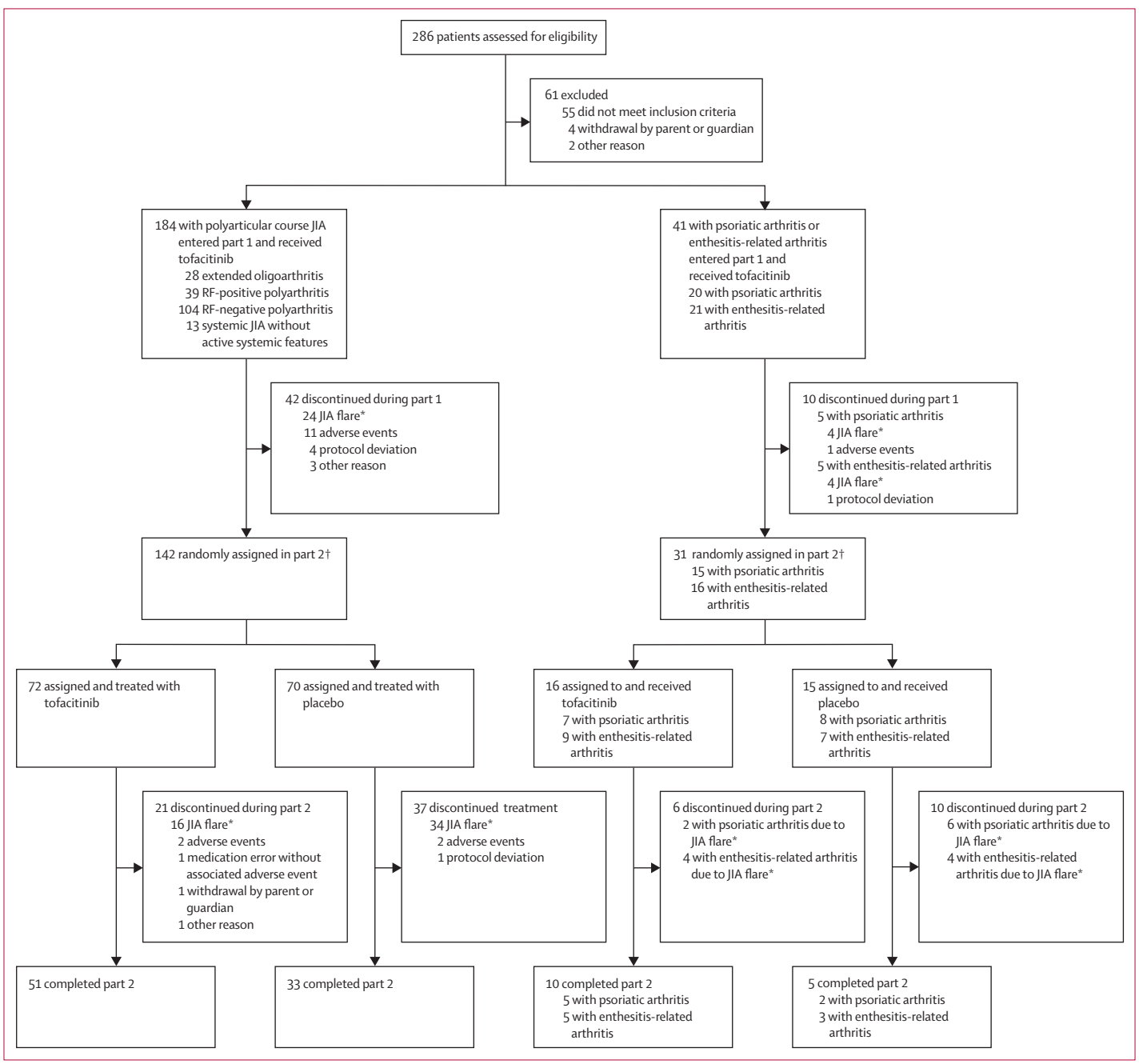

Figure 1: **Trial profile**
Patients who participated in this trial had the option of enrolling in the tofacitinib JIA open-label long-term extension trial (NCT01500551, appendix pp 7–8, which was designed to evaluate the long-term safety and tolerability of tofacitinib in patients with JIA.*Insufficient clinical response was listed in the Case Report Form if the patient discontinued due to JIA flare.22 †Patients who achieved JIA/ACR30 response or better at week 18 were eligible for randomisation in part 2; in total, 185 patients completed part 1 (polyarticular course JIA n=151; psoriatic arthritis or enthesitis-related arthritis n=34), however, at week 18, 12 patients discontinued (polyarticular course JIA n=9; psoriatic arthritis or enthesitis-related arthritis n=3): 11 due to JIA insufficient clinical response (polyarticular course JIA n=8, psoriatic arthritis or enthesitis-related arthritis n=3), and one with polyarticular course due to protocol deviation. ACR=American College of Rheumatology. JIA=juvenile idiopathic arthritis. RF=rheumatoid factor.

PRINTO and PRCSG officers, with medical writing support from CMC Connect, funded by Pfizer.

Results

Between June 10, 2016, and May 16, 2019, among 286 screened patients, 225 (79%) were enrolled and received open-label tofacitinib in part 1, 184 (82%) with polyarticular course JIA (primary analyses; figure 1), and 20 (9%) with psoriatic arthritis and 21 (9%) with enthesitis-related arthritis (exploratory analyses; figure 1). Demographics and baseline disease characteristics are presented for all patients enrolled in part 1 and stratified by JIA category (table 1). Median disease duration in the 225 patients was 2·5 years (IQR 1·0–5·6). Most patients had rheumatoid factor-negative polyarthritis (104 [46%]) or rheumatoid factor-positive polyarthritis (39 [17%]) and 1 (<1%) patient had history of uveitis that was inactive at the time of enrolment.

At baseline, 221 (98%) of 225 patients had JADAS high-disease activity. 147 (65%) patients received concomitant methotrexate, and oral glucocorticoids (maximum per-protocol dose 0·2 mg/kg per day or 10 mg per day) were taken by 73 (32%) patients. Previous conventional synthetic DMARD and biological DMARD use was reported in 206 (92%) and 85 (38%) patients, respectively.

	All patients (n=225)	Patients with polyarticular course JIA enrolled for primary outcome (n=184)				Patients with psoriatic arthritis or enthesitis-related arthritis enrolled for exploratory outcomes (n=41)	
		Extended oligoarthritis (n=28)	RF-positive polyarthritis (n=39)	RF-negative polyarthritis (n=104)	Systemic JIA* (n=13)	Psoriatic arthritis (n=20)	Enthesitis-related arthritis (n=21)
Patient characteristics							
Sex							
Female	169 (75%)	19 (68%)	35 (90%)	83 (80%)	5 (38%)	15 (75%)	12 (57%)
Male	56 (25%)	9 (32%)	4 (10%)	21 (20%)	8 (62%)	5 (25%)	9 (43%)
Age, years	13·0 (9·0–15·0)	11·5 (6·5–15·0)	15·0 (12·0–16·0)	12·0 (8·0–15·0)	10·0 (8·0–14·0)	14·5 (12·0–16·0)	13·0 (11·0–16·0)
2 to <6	22 (10%)	6 (21%)	0	14 (13%)	2 (15%)	0	0
6 to <12	64 (28%)	8 (29%)	5 (13%)	34 (33%)	6 (46%)	4 (20%)	7 (33%)
12 to <18	139 (62%)	14 (50%)	34 (87%)	56 (54%)	5 (38%)	16 (80%)	14 (67%)
Age at diagnosis, years	8·0 (4·0–12·3)	3·9 (1·9–11·1)	12·8 (9·5–14·3)	6·1 (3·6–9·9)	3·5 (2·8–5·9)	12·0 (9·3–14·0)	10·1 (7·9–13·0)
Disease duration, years	2·5 (1·0–5·6)	4·0 (1·6–7·7)	1·8 (1·0–3·6)	3·5 (1·0–6·7)	5·4 (2·1–8·2)	1·5 (1·0–2·8)	1·9 (0·8–4·0)
Bodyweight, kg							
<40	84 (37%)	12 (43%)	9 (23%)	46 (44%)	9 (69%)	2 (10%)	6 (29%)
≥40	141 (63%)	16 (57%)	30 (77%)	58 (56%)	4 (31%)	18 (90%)	15 (71%)
Race							
White	196 (87%)	26 (93%)	29 (74%)	95 (91%)	11 (85%)	17 (85%)	18 (86%)
Black or African American	5 (2%)	0	3 (8%)	1 (1%)	0	0	1 (5%)
Other	24 (11%)	2 (7%)	7 (18%)	8 (8%)	2 (15%)	3 (15%)	2 (10%)
Disease activity measures							
Physician's global evaluation of overall disease activity†	6·0 (4·5–7·5)	6·8 (4·8–7·5)	6·5 (5·5–7·5)	6·5 (4·8–7·8)	7·5 (5·5–8·0)	5·0 (4·0–7·0)	6·0 (4·5–7·0)
Number of joints with active arthritis‡	10·0 (6·0–15·0)	7·0 (5·0–11·0)	11·0 (8·0–19·0)	10·0 (7·0–18·0)	9·0 (7·0–15·0)	11·0 (4·5–15·5)	7·0 (5·0–11·0)
Number of joints with limitation of motion§	6·0 (3·0–10·0)	5·0 (2·5–7·5)	4·0 (2·0–9·0)	6·0 (4·0–11·0)	9·0 (7·0–15·0)	5·0 (3·0–8·0)	5·0 (3·0–7·0)
CHAQ-DI score¶	0·9 (0·3–1·5)	1·0 (0·3–1·6)	1·3 (0·4–1·9)	0·8 (0·3–1·4)	1·6 (1·3–2·0)	0·5 (0·3–0·8)	0·6 (0·4–1·3)
Patient or parent assessment of overall wellbeing‖	5·0 (3·0–7·0)	5·8 (4·0–7·0)	5·0 (2·5–6·0)	5·0 (3·0–7·0)	5·5 (3·5–8·0)	4·0 (3·0–6·5)	5·0 (2·5–6·5)
JADAS**	20·1 (16·2–26·6)	20·6 (16·6–24·6)	22·2 (18·8–26·9)	20·7 (16·6–28·8)	23·7 (17·2–27·2)	15·5 (13·6–19·6)	16·6 (13·2–18·7)
Duration of morning stiffness, min	30·0 (15·0–60·0)	30·0 (7·5–75·0)	30·0 (20·0–60·0)	30·0 (15·5–60·0)	45·0 (30·0–60·0)	30·0 (10·0–60·0)	30·0 (15·0–60·0)
Laboratory parameters							
CRP††, mg/dL	0·3 (0·1–1·0)	0·2 (0·1–0·9)	0·6 (0·1–1·6)	0·2 (0–0·9)	0·6 (0·2–2·6)	0·2 (0·1–0·5)	0·1 (0–0·9)
ESR‡‡, mm/h	17·0 (10·0–32·0)	18·5 (10·0–32·5)	26·0 (10·0–40·0)	16·0 (10·0–26·5)	25·0 (8·0–45·0)	14·0 (10·0–28·5)	12·0 (7·0–29·0)

Data are median (IQR) or n (%). CHAQ-DI=Childhood Healthcare Questionnaire-Disability Index. CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. JADAS=Juvenile Arthritis Disease Activity Score in 27 joints, based on CRP. JIA=juvenile idiopathic arthritis. RF=rheumatoid factor. *Without active systemic features at enrolment. †Scores could range from 0 to 10, with higher scores indicating more disease activity.[20] ‡71 joints were assessed.[27] §67 joints were assessed.[27] ¶Scores could range from 0 to 3, with higher scores indicating more disability.[21] ‖Scores could range from 0 to 10, with higher scores indicating worse wellbeing.[20] **Scores could range from 0 to 57, with higher scores indicating more disease activity.[25] ††Normal reference range was 0–0·287 mg/dL. ‡‡Normal reference range was 0–20 mm/h.

Table 1: **Demographic and baseline disease characteristics of patients receiving tofacitinib in part 1, overall, and stratified by JIA category**

Patient demographics and disease characteristics at part 1 baseline for patients who were randomly assigned in part 2 of the study are shown in the appendix (pp 22–24).

Of 184 patients with polyarticular course JIA enrolled in part 1 (weeks 0–18), 142 (77%) were randomly assigned in part 2 to receive tofacitinib (n=72) or placebo (n=70; figure 1A). In patients with polyarticular course JIA, JIA flare rate in part 2 (weeks 18–44) was statistically significantly lower with tofacitinib (21 [29%] of 72 patients) than with placebo (37 [53%] of 70 patients; p=0·0031; figure 2A). These results were supported by a sensitivity

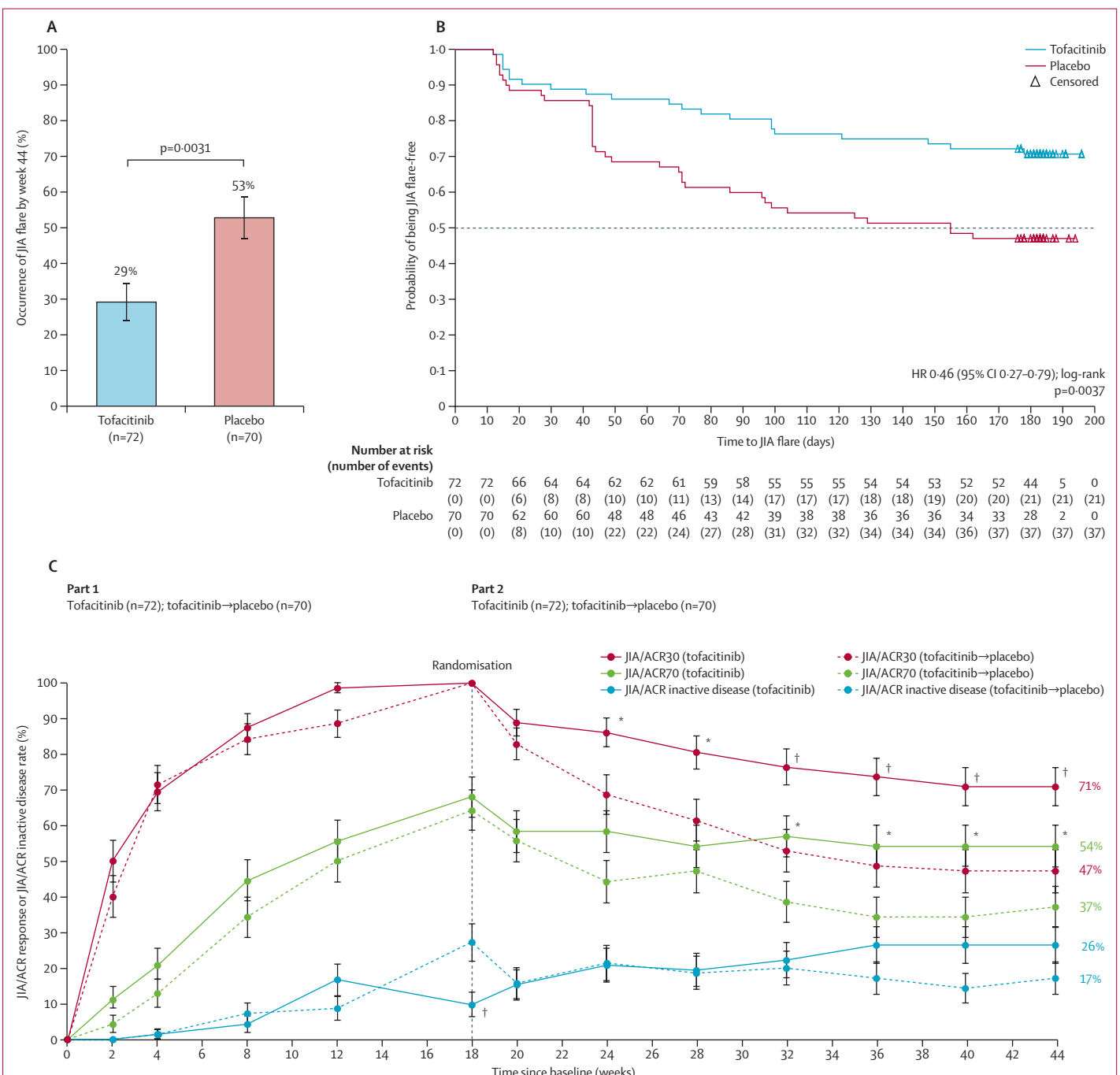

Figure 2: **Efficacy of tofacitinib versus placebo in patients with polyarticular course JIA who were randomly assigned in part 2 of the study**
(A) JIA flare rate by week 44 (primary endpoint) in part 2. (B) Time to JIA flare in part 2. (C) JIA/ACR30/70 response and JIA/ACR inactive disease rates during parts 1 and 2 of the study. Error bars in (A) and (C) represent standard error. ACR=American College of Rheumatology. JIA=juvenile idiopathic arthritis. HR=hazard ratio. *p<0·05. †p<0·01.

analysis using the Cochran-Mantel-Haenszel test with a difference of proportions (tofacitinib minus placebo) of –25% (95% CI –40% to –10%; p=0·0013). The prespecified subgroup analysis is shown in the appendix (p 9).

Time to JIA flare during part 2 was significantly shorter with placebo (median 155 days, 95% CI 86·0–not evaluable) than with tofacitinib (median not evaluable because 71% of patients remained flare-free; hazard ratio 0·46, 95% CI 0·27–0·79; log-rank p=0·0037; figure 2B).

Achievement of JIA/ACR30/70 response occurred as early as week 2 and JIA/ACR inactive disease as early as week 4 (appendix p 10). At the end of part 1, 142 (77%) of 184 and 94 (51%) of 184 patients had achieved JIA/ACR30 and JIA/ACR70 response rates, respectively (appendix pp 10–11).

During part 2, JIA/ACR30 response rates were statistically significantly higher from week 24 and JIA/ACR70 response rates were statistically significantly higher from week 32 in the tofacitinib group than in the placebo group (figure 2C); JIA/ACR inactive disease rates were not statistically signicantly higher in the tofacitinib group than in the placebo group. By week 44, JIA/ACR inactive disease was achieved in 19 (26%) of 72 patients in the tofacitinib and 12 (17%) of 70 patients in the placebo group (figure 2C); and clinical remission was achieved in three (4%) patients in each treatment group. JIA/ACR30/50/70 response rates at week 44 were statistically significantly higher with tofacitinib than with placebo (appendix p 11). The subgroup analysis of JIA/ACR 30 response rate at week 44 is shown in the appendix (p 12).

JIA/ACR50/90/100 response rates were higher with tofacitinib than with the placebo throughout part 2 (appendix p 13). From week 2 of part 1, improvements in all JIA/ACR core set variables occurred and were at least maintained in part 2 (appendix pp 14–15). During part 2, physical functioning, assessed by mean change in CHAQ-DI score, improved with continued tofacitinib use but not with placebo (least squares mean difference CHAQ-DI at week 44: tofacitinib –0·09 [95% CI –0·17 to –0·01] vs placebo 0·03 [–0·06 to 0·12], p=0·029; type 1 error-controlled endpoint; appendix p 16).

In observed analyses (ie, observed case analysis with no imputation for missing data), there was an early and rapid reduction in mean JADAS disease activity level during part 1 (figure 3A), and 48 (29%) of 165 patients reached JADAS minimum disease activity by week 12 with six (4%) of 165 patients reaching JADAS inactive disease (appendix p 17). At week 18, JADAS minimum disease activity was achieved in 68 (44%) of 154 patients and JADAS inactive disease in 12 (8%) of 154 patients (appendix p 17). During part 2, JADAS minimum disease activity and JADAS inactive disease were maintained with continued tofacitinib treatment (appendix p 17). At week 44, JADAS minimum disease activity was achieved by 34 (47%) of 72 patients in the tofacitinib group and 23 (33%) of 70 patients in the placebo group; JADAS inactive disease was achieved by 13 (18%) patients in the tofacitinib group and seven (10%) in the placebo group.

In the prespecified exploratory efficacy analysis of patients with psoriatic arthritis (20 [9%] of 225 patients) and enthesitis-related arthritis (21 [9%]), JIA flare rate in part 2 at week 44 was: two (29%) of seven patients in the tofacitinib group and six (75%) of eight patients in the

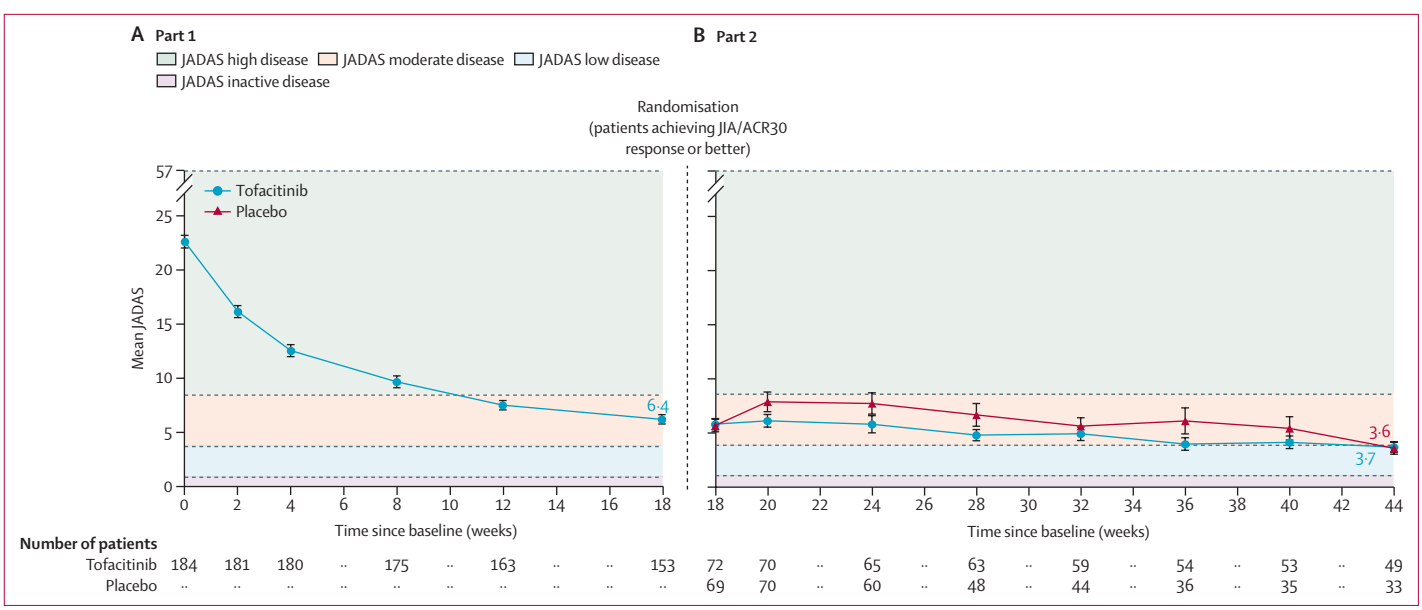

Figure 3: **Mean JADAS during part 1 (A) and 2 (B) of the study in patients with polyarticular course JIA**

Scores could range from 0 to 57, with higher scores indicating more disease activity.[25] Error bars indicate standard error. Dashed lines indicate thresholds for different JADAS disease activity level cutoffs. ACR= American College of Rheumatology. JADAS=Juvenile Arthritis Disease Activity Score in 27 joints, based on C-reactive protein. JIA=juvenile idiopathic arthritis.

placebo group for patients with psoriatic arthritis; and four (44%) of nine patients and four (57%) of seven patients, respectively, in patients with enthesitis-related arthritis. JADAS decreased during part 1 and remained stable during part 2 (appendix p 18).

In patients with polyarticular course JIA, psoriatic arthritis, or enthesitis-related arthritis, safety was generally similar in those receiving tofacitinib or placebo (tables 2, 3). Most adverse events were mild or moderate, with severe adverse events reported in five (2%) of 225 patients in the entire tofacitinib exposure period, all of which occurred in part 1. Additionally, severe adverse events were reported in three (4%) of 85 patients in the placebo group in part 2.

During part 1, hepatic events were reported in three patients (1%; mild liver enzyme elevations in two patients, moderate liver enzyme elevations in one patient) in the tofacitinib group. These events were adjudicated and considered possible (mild in one patient) or probable (mild in one patiet and moderate in another patient)

	Part 1	Part 2		Entire tofacitinib exposure period*
	Tofacitinib (n=225)	Tofacitinib (n=88)	Placebo (n=85)	Tofacitinib (n=225)
Adverse events	153 (68%)	68 (77%)	63 (74%)	189 (84%)
Incidence rate per 100 patient-years (95% CI)	..	371·7 (288·6–471·2)	417·8 (321·0–534·5)	394·0 (339·9–454·4)
Serious adverse events	7 (3%)	1 (1%)	2 (2%)	9 (4%)
Incidence rate per 100 patient-years (95% CI)	..	2·4 (0·1–13·4)	6·0 (0·7–21·8)	7·3 (3·4–13·9)
Severe adverse events	5 (2%)	0	3 (4%)	5 (2%)
Permanent discontinuation from study due to adverse events	26 (12%)	16 (18%)	29 (34%)	49 (22%)
Incidence rate per 100 patient-years (95% CI)	..	39·6 (22·6–64·3)	94·2 (63·1–135·3)	40·9 (30·3–54·1)
Temporary dose reduction or temporary hold due to adverse events	20 (9%)	9 (10%)	8 (9%)	25 (11%)
Most common adverse events by preferred term (≥10% in any treatment group)				
Upper respiratory tract infection	24 (11%)	13 (15%)	9 (11%)	34 (15%)
Disease progression	5 (2%)	8 (9%)	13 (15%)	13 (6%)
JIA exacerbation	6 (3%)	3 (3%)	12 (14%)	9 (4%)
Adverse events of special interest†				
Deaths	0	0	0	0
Hepatic events‡	3 (1%)	0	0	3 (1%)
Herpes zoster (non-serious and serious)‡§	2 (1%)	0	0	2 (1%)
Incidence rate per 100 patient-years (95% CI)	..	..	..	1·6 (0·2–5·9)
Serious infection	3 (1%)	1 (1%)¶	1 (1%)	4 (2%)¶
Incidence rate per 100 patient-years (95% CI)	..	..	3·0 (0·1–16·8)	2·4 (0·5–7·1)
Creatine kinase >2·0 × ULN	12/224 (5%)	2 (2%)	2 (2%)	13/224 (6%)
Haemoglobin <0·8 × LLN	1/224 (<0·5%)	1/87 (1%)	3 (4%)	2/224 (1%)
Lymphocytes >1·2 × ULN	2/224 (1%)	1/87 (1%)	0	3/224 (1%)
Neutrophils >1·2 × ULN	18/224 (8%)	7/87 (8%)	5 (6%)	19/224 (8%)
AST ≥1·0 × ULN	25 (11%)	12 (14%)	9 (11%)	35 (16%)
ALT ≥1·0 × ULN	33 (15%)	14 (16%)	11 (13%)	37 (16%)
HDL cholesterol <0·8 × LLN	2/223 (1%)	0‖	2/61 (3%)	2/223 (1%)
LDL cholesterol >1·2 × ULN	4/87 (5%)	0**	0††	4/87 (5%)
Cholesterol >1·3 × ULN	2/223 (1%)	0‡‡	0§§	2/223 (1%)

Data are n (%) or n/N (%), unless otherwise specified. Patients that had an event in both parts of the study are only counted once for the entire tofacitinib exposure period. ALT=alanine aminotransferase. AST=aspartate aminotransferase. JIA=juvenile idiopathic arthritis. LLN=lower limit of normal. ULN=upper limit of normal. *Placebo exposure might have contributed a maximum of 28 days to the risk period for the following events: adverse events, serious adverse events, permanent discontinuations due to adverse events, and adverse events of special interest except hepatic events; for other events reported, those occurring during placebo exposure were excluded. †During the trial, there were no reports of the following adverse events of special interest: gastrointestinal perforation, interstitial lung disease, major adverse cardiovascular events, macrophage activation syndrome, malignancies, opportunistic infection, thrombotic events, or tuberculosis. ‡Adjudicated events. §Both incidences were mild, monodermatomal, and non-serious, and neither met opportunistic infection criteria. ¶One serious adverse event of pilonidal cyst repair was coded to surgical procedures instead of infections and was inadvertently not identified as a serious infection. The serious adverse event was adjudicated and was determined to not meet opportunistic infection criteria. It is presented in the table as a serious infection; however, it was not included in the incidence rate calculation. ‖Assessed in 70 patients. **Assessed in five patients. ††Assessed in four patients. ‡‡Assessed in 71 patients. §§Assessed in 61 patients.

Table 2: **Summary of treatment-emergent adverse events and laboratory abnormalities in patients with polyarticular course JIA, psoriatic arthritis, or enthesitis-related arthritis**

	Part 1		Part 2	
	Tofacitinib (n=225)		Tofacitinib (n=88)	Placebo (n=85)
	Baseline	Week 18	Week 44	Week 44
Creatine kinase, U/L	72·0 (45·0–96·0)	97·0 (72·0–130·0)*	104·0 (83·0–159·0)†	80·0 (56·0–109·0)‡
Haemoglobin, g/dL	12·4 (11·7–13·3)	12·8 (12·0– 13·4)§	12·6 (12·2–13·2)¶	12·6 (12·3–13·5)‡
Lymphocytes, 10^3 cells per mm^3	2·1 (1·7–2·6)	2·0 (1·6–2·6)§	1·9 (1·6–2·4)¶	1·8 (1·7– 2·4)‡
Neutrophils, 10^3 cells per mm^3	4·4 (3·1–5·6)	3·8 (2·9–5·1)§	3·6 (2·9–4·4)¶	3·6 (2·8–4·5)‡
AST, U/L	20·0 (17·0–24·0)	22·0 (18·0–26·0)‖	23·0 (19·0–28·0)†	19·5 (17·0–26·0)‡
ALT, U/L	13·0 (10·0–17·0)	13·0 (11·0–19·0)*	15·0 (12·0–20·0)†	13·0 (11·0–18·0)‡
HDL cholesterol, mg/dL	50·1 (42·9–57·9)**	55·6 (47·5–64·1)††	54·8 (47·5–64·1)†	48·5 (44·8–52·0)‡
Indirect LDL cholesterol, mg/dL	81·0 (64·0–94·0)**	81·9 (67·2–100·0)*	84·7 (68·0–106·9)†	79·0 (57·9–101·0)‡
Cholesterol, mg/dL	151·0 (131·0–169·5)‡‡	158·0 (139·8–179·0)††	157·9 (143·0–185·3)§§	150·0 (130·9–177·0)‡

Data are median (IQR). ALT=alanine aminotransferase. AST=aspartate aminotransferase. JIA=juvenile idiopathic arthritis. *Assessed in 186 patients. †Assessed in 58 patients. ‡Assessed in 38 patients. §Assessed in 176 patients. ¶Assessed in 57 patients. ‖Assessed in 183 patients. **Assessed in 222 patients. ††Assessed in 187 patients. ‡‡Assessed in 223 patients. §§Assessed in 59 patients.

Table 3: **Summary of laboratory values in patients with polyarticular course JIA, psoriatic arthritis, or enthesitis-related arthritis**

drug-induced liver injury. All of the hepatic events occurred before week 8 of treatment and none of the events met Hy's law criteria. Serious infections were reported in three patients (1%; one with pneumonia, one with epidural empyema and sinusitis in a patient with a history of craniosynostosis repair, and one with appendicitis). Herpes zoster was reported in two patients (1%); both cases were mild, monodermatomal, and non-serious, and neither met opportunistic infection criteria. There were no cases of active uveitis.

During part 2, a serious infection (appendicitis) was reported in one (1%) of 85 patients receiving placebo. In one (1%) of 88 tofacitinib-treated patients, a serious infection of pilonidal cyst repair occurred; this serious adverse event did not meet opportunistic infection criteria. Active uveitis was reported at week 24 in one patient in the placebo group.

In part 1, temporary dose reductions or temporary hold due to adverse events occurred in 20 (9%) of 225 patients. In part 2, temporary dose reductions or temporary hold due to adverse events occurred in nine (10%) of 88 patients in the tofacitinib group and eight (9%) of 85 patients in the placebo group. In part 1, permanent discontinuations due to adverse events occurred in 26 (12%) of 225 patients. In part 2, permanent discontinuations due to adverse events occurred in 16 (18%) of 88 patients receiving tofacitinib and 29 (34%) of 85 patients receiving placebo. In both parts 1 and 2, disease progression and juvenile idiopathic arthritis were the most common adverse events that led to discontinuation. The majority of patients who discontinued the trial enrolled in the open-label, long-term extension trial (appendix pp 7–8).

During the trial, there were no reports of the following adverse events of special interest: death, gastrointestinal perforation, interstitial lung disease, major adverse cardiovascular events, macrophage activation syndrome, malignancies, opportunistic infection, thrombotic events, or tuberculosis.

The most common adverse events by system organ class were infections and infestations, reported in 107 (48%) of 225 patients in the entire tofacitinib exposure period (appendix pp 25–26), 77 (72%) of which were mild. Serious infections occurred in 4 (2%) of 225 tofacitinib-treated patients (table 2).

In part 2, laboratory abnormality rates and median laboratory values were generally similar with tofacitinib and placebo (tables 2, 3). Laboratory data are presented in terms of median change from part 1 baseline to week 18 and week 44, and median change from part 2 baseline to week 44 in the appendix (p 27).

Discussion

Tofacitinib, the first oral JAK inhibitor evaluated in patients with JIA, improved disease signs and symptoms in a rapid and sustained manner. This clinical trial met its primary endpoint: JIA flare rate was significantly lower with tofacitinib than with placebo. Improvements were seen with tofacitinib versus placebo in secondary endpoints, including JIA/ACR response and JIA/ACR inactive disease rates, JADAS, and change in CHAQ-DI.

JIA/ACR response and JIA flare rates with tofacitinib were comparable with those in randomised, double-blind, withdrawal or parallel-group studies of parenteral biological DMARDs in patients with polyarticular course JIA.[5–7,10,11,28]

Despite the short pharmacokinetic half-life of tofacitinib[19] and the reversibility of pharmacodynamic effects after up to 6 weeks of discontinuation,[29] patients receiving placebo after open-label tofacitinib had a relatively long median time to flare (>5 months). This finding might indicate a prolonged biological effect of tofacitinib, as observed with biological DMARDs.[9,11]

Rates of JIA/ACR inactive disease were similar to those in previous phase 3 trials of biological DMARDs in patients with JIA.[5,9,11] The stronger concept of JIA/ACR clinical remission (inactive disease for 6 continuous months) was rare (achieved in <5% of patients), which

might be expected given the relatively short duration of the trial (44 weeks).

This trial enrolled a higher proportion of rheumatoid factor-positive patients than would be expected per the general JIA population,[12] as observed in previous trials assessing biological DMARDs in patients with polyarticular course JIA.[5–7,10,11,28] Patients with rheumatoid factor-positive polyarthritis, the childhood counterpart of rheumatoid arthritis, are more likely to not respond to previous therapies[30] and thus remain eligible for JIA trials. Compared with patients in early biological DMARD studies in polyarticular course JIA,[5–7,28] patients in this tofacitinib trial had a shorter disease duration and less severe JIA features (eg, fewer active joints, lower CRP levels) at enrolment. This shorter disease duration and less severe JIA is probably due to the wider availability of approved biological DMARDs, at least in higher-income countries,[14] and the tendency, as per the treat-to-target approach,[4] to treat patients with JIA with biological DMARDs in the earlier phase of the disease.

Few patients with psoriatic arthritis or enthesitis-related arthritis were enrolled in this trial, limiting the comparison of tofacitinib and placebo in these populations. However, open-label tofacitinib treatment showed rapid and sustained improvement in disease activity similar to that in polyarticular course JIA.

There were no new potential safety risks identified for tofacitinib in children and adolescents. Indeed, overall, safety was consistent with that previously reported in patients with rheumatoid arthritis.[16] Notably, rates of adverse events and serious adverse events were similar between both treatment groups in part 2 of the study. Elevations that were more than one times the upper limit of normal in aspartate aminotransferase and alanine aminotransferase occurred at lower rates than reported in adults with rheumatoid arthritis.[16] However, the follow-up length of this trial in patients with JIA was too short to assess long-term safety, including occurrence of adverse events of special interest.

Limitations of the trial must be considered. Tofacitinib efficacy was assessed indirectly by occurrence of JIA flare. Due to the large number of placebo-treated patients who met flare criteria in part 2 of the study and were, therefore, required to discontinue, observed differences in efficacy between tofacitinib versus placebo might be reduced. The trial population was relatively small and predominantly White, although from a diverse geographical distribution. Also, it was not possible to detect rare adverse events. An ongoing, open-label, long-term extension trial (NCT01500551) might provide further information on the efficacy and safety of tofacitinib in patients with JIA. Additionally, it will be important to observe the long-term safety of tofacitinib in routine care.

In conclusion, in this phase 3 trial, tofacitinib resulted in a rapid and sustained clinical improvement in polyarticular course JIA disease activity with no new potential safety risks identified. These findings suggest a favourable benefit–risk balance in patients with polyarticular course JIA treated with oral tofacitinib. It will be important to confirm these results in clinical practice and with long-term follow-up. New treatment options are important in the treat-to-target era, and new oral therapies are particularly relevant for children and adolescents, who might prefer to avoid injections.

Contributors

NR, HIB, DJL, and AM (from Paediatric Rheumatology International Trials Organisation [PRINTO] and Pediatric Rheumatology Collaborative Study Group [PRCSG]) and HBP, KSK, AW, RZ, M-AH, and RMS (from Pfizer) contributed to the study conception and design. NR, HIB, OS, TVT, CAM, AS, YV, KM, LG, IT, LI, RJ, DJK, BS, SSV, SP, EZ, YBA, VC, ML, KN, HS, HT, YU, DOV, DJL, and AM (from PRINTO and PRCSG), and HBP, KSK, AW, CC, RZ, IL, and RMS (from Pfizer) were involved in the acquisition of data. All authors had access to the data, and NR and RMS accessed and verified the raw data reported in this Article. All authors, including those employed by the sponsor, were involved in the analysis and interpretation of data and drafting the Article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

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Declaration of interests

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Data sharing

Upon request, and subject to certain criteria, conditions, and exceptions, Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies done for medicines, vaccines, and medical devices (1) for indications that have been approved in the USA, EU, or both, or (2) in programmes that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data can be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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