Baricitinib in juvenile idiopathic arthritis: an international, phase 3, randomised, double-blind, placebo-controlled, withdrawal, efficacy, and safety trial

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Summary

Background Juvenile idiopathic arthritis can be refractory to some or all treatment regimens, therefore new medications are needed to treat this population. This trial assessed the efficacy and safety of baricitinib, an oral Janus kinase 1/2-selective inhibitor, versus placebo in patients with juvenile idiopathic arthritis.

Methods This phase 3, randomised, double-blind, placebo-controlled, withdrawal, efficacy, and safety trial was conducted in 75 centres in 20 countries. We enrolled patients (aged 2 to <18 years) with polyarticular juvenile idiopathic arthritis (positive or negative for rheumatoid factor), extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or juvenile psoriatic arthritis, and an inadequate response (after ≥12 weeks of treatment) or intolerance to one or more conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs). The trial consisted of a 2-week safety and pharmacokinetic period, a 12-week open-label lead-in period (10 weeks for the safety and pharmacokinetic subcohort), and an up to 32-week placebo-controlled double-blind withdrawal period. After age-based dosing was established in the safety and pharmacokinetic period, patients received a once-daily 4 mg adult-equivalent dose of baricitinib (tablets or suspension) in the open-label lead-in period. Patients meeting Juvenile Idiopathic Arthritis-American College of Rheumatology (JIA-ACR) 30 criteria (JIA-ACR30 responders) at the end of the open-label lead-in (week 12) were eligible for random assignment (1:1) to receive placebo or continue receiving baricitinib, and remained in the double-blind withdrawal period until disease flare or up to the end of the double-blind withdrawal period (week 44). Patients and any personnel interacting directly with patients or sites were masked to group assignment. The primary endpoint was time to disease flare during the double-blind withdrawal period and was assessed in the intention-to-treat population of all randomly assigned patients. Safety was assessed in all patients who received at least one dose of baricitinib throughout the three trial periods. For adverse events in the double-blind withdrawal period, exposure-adjusted incidence rates were calculated. The trial was registered on ClinicalTrials.gov, NCT03773978, and is completed.

Findings Between Dec 17, 2018 and March 3, 2021, 220 patients were enrolled and received at least one dose of baricitinib (152 [69%] girls and 68 [31%] boys; median age 14·0 years [IQR 12·0–16·0]). 219 patients received baricitinib in the open-label lead-in period, of whom 163 (74%) had at least a JIA-ACR30 response at week 12 and were randomly assigned to placebo (n=81) or baricitinib (n=82) in the double-blind withdrawal period. Time to disease flare was significantly shorter with placebo versus baricitinib (hazard ratio 0·241 [95% CI 0·128–0·453], p<0·0001). Median time to flare was 27·14 weeks (95% CI 15·29–not estimable) in the placebo group, and not evaluable for patients in the baricitinib group (<50% had a flare event). Six (3%) of 220 patients had serious adverse events during the safety and pharmacokinetic period or open-label lead-in period. In the double-blind withdrawal period, serious adverse events were reported in four (5%) of 82 patients (incidence rate [IR] 9·7 [95% CI 2·7–24·9] per 100 patient-years at risk) in the baricitinib group and three (4%) of 81 (IR 10·2 [2·1–29·7]) in the placebo group. Treatment-emergent infections were reported during the safety and pharmacokinetic or open-label lead-in period in 55 (25%) of 220 patients, and during the double-blind withdrawal period in 31 (38%) of 82 (IR 102·1 [95% CI 69·3–144·9]) in the baricitinib group and 15 (19%) of 81 (IR 59·0 [33·0–97·3]) in the placebo group. Pulmonary embolism was reported as a serious adverse event in one patient (1%; IR 2·4 [95% CI 0·1–13·3]) in the baricitinib group in the double-blind withdrawal period, which was judged to be related to study treatment.

Interpretation Baricitinib was efficacious with an acceptable safety profile in the treatment of polyarticular juvenile idiopathic arthritis, extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, and juvenile psoriatic arthritis, after inadequate response or intolerance to standard therapy.

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*Other members of the JUVE-BASIS investigators group are listed at the end of the Article; the full list of JUVE-BASIS investigators is included in the appendix (pp 7–14)

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See **Online** for appendix

Research in context

Evidence before this study

Juvenile idiopathic arthritis is a heterogeneous group of idiopathic autoimmune childhood arthritides that can have debilitating, long-lasting effects on functional ability and quality of life if untreated. Current treatment options include nonsteroidal anti-inflammatory drugs, glucocorticoids, conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs), and small molecules. However, juvenile idiopathic arthritis can be refractory to some or all currently accepted treatment regimens, with approximately a third of patients on first-line biologic DMARDs switching to at least one other treatment in a 2-year period. We searched PubMed on March 18, 2023, with no date limits or language restrictions, using the terms ((janus kinase inhibitor [All Fields]) OR (JAK inhibitor [All Fields]) OR (baricitinib [All Fields]) OR (tofacitinib [All Fields]) OR (upadacitinib [All Fields]) OR (filgotinib [All Fields])) AND ((juvenile idiopathic arthritis [MeSH Terms]) OR (juvenile idiopathic arthritis [All Fields])) AND (clinical trial [Filter]). The search identified two clinical trials (a phase 1, open-label, multicentre study, and a double-blind, placebo-controlled, randomised, phase 3, withdrawal trial) of tofacitinib in patients with juvenile idiopathic arthritis. The phase 3 trial reported that disease flare rate, by end of the withdrawal period, was significantly lower with tofacitinib (29%) than with placebo (53%). No other phase 3 trials of baricitinib in juvenile idiopathic arthritis were identified.

Added value of this study

Baricitinib, a JAK1/2 inhibitor, exhibited a favourable risk–benefit profile for the treatment of juvenile idiopathic arthritis, with improvements in clinical measures and patient-reported outcomes compared with placebo. This trial met its primary endpoint, in that time to juvenile idiopathic arthritis flare was significantly longer in patients receiving baricitinib than in those receiving placebo during a double-blind withdrawal period of the study. Secondary efficacy endpoints related to disease activity, functional ability, and quality of life were more favourable with baricitinib than placebo. The safety profile of baricitinib in children and adolescents with juvenile idiopathic arthritis was consistent with the established profile in other baricitinib indications in adults.

Implications of all the available evidence

The results of this study indicate a favourable profile for baricitinib when used for the treatment of patients with juvenile idiopathic arthritis after failure of conventional synthetic or biologic DMARDs. Furthermore, the once-daily oral administration of baricitinib might provide improved adherence rates as compared with other oral medications requiring more frequent administration. The holistic improvements with JAK inhibition in patients with juvenile idiopathic arthritis could provide insights into disease activity that highlight unmet needs in treatment options for this patient population.

Introduction

Juvenile idiopathic arthritis is a heterogeneous group of rheumatic diseases with onset by age 16 years, as defined by the International League Against Rheumatism (ILAR).[1,2] A typical feature of juvenile idiopathic arthritis is articular inflammation of the synovium, which produces joint swelling, pain, and stiffness.[3] If left untreated, juvenile idiopathic arthritis is associated with poor health-related quality of life (HQoL) and can result in severe functional impairment and disability.[1] With approximately 2 million children affected worldwide, juvenile idiopathic arthritis is among the most common paediatric chronic diseases.[4] Treatments for juvenile idiopathic arthritis include nonsteroidal anti-inflammatory drugs, systemic glucocorticoids, and conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs), with approximately a third of patients on first-line biologic DMARDs switching to at least one other treatment in a 2-year period.[5–11]

Polyarticular course juvenile idiopathic arthritis includes polyarticular juvenile idiopathic arthritis, extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, and juvenile psoriatic arthritis. The pathogenesis of polyarticular juvenile idiopathic arthritis is considered similar to types of inflammatory arthritis diagnosed in adults, such as rheumatoid arthritis.[1] Likewise, enthesitis-related arthritis and juvenile psoriatic arthritis are considered the paediatric forms of non-radiographic axial spondyloarthritis and psoriatic arthritis in adults, respectively.[12]

Several inflammatory cytokines that are implicated in juvenile idiopathic arthritis pathogenesis (eg, interleukin [IL]-6 and tumour necrosis factor [TNF]) signal through pathways mediated by Janus kinases (JAKs).[13,14] A phase 3 trial of the oral JAK inhibitor tofacitinib, administered twice a day, in patients with juvenile idiopathic arthritis (aged 2–17 years) showed that the proportion of patients with juvenile idiopathic arthritis flare, during a study withdrawal period, was significantly lower with tofacitinib (21 [29%] of 72 patients) than with placebo (37 [53%] of 70 patients; hazard ratio [HR] 0·46, 95% CI 0·27–0·79; p=0·0031).[15] Baricitinib, an oral JAK1/2-selective inhibitor, has shown clinical safety and efficacy in adult patients (aged ≥18 years) with rheumatoid arthritis in four completed phase 3 clinical trials.[16]

Here, we report on the JUVE-BASIS trial, which assessed the efficacy and safety of baricitinib in children with polyarticular juvenile idiopathic arthritis, extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or juvenile psoriatic arthritis, after failure of at least one conventional synthetic or biologic DMARD.

Methods

Study design

JUVE-BASIS was a phase 3, randomised, double-blind, placebo-controlled, withdrawal, efficacy, and safety trial conducted in 75 centres in 20 countries (appendix pp 7–14, 26), including members of the Paediatric Rheumatology International Trials Organisation (PRINTO). PRINTO is a not-for-profit network that has facilitated previous clinical trials in paediatric rheumatology.[17] The current study consisted of a 2-week safety and pharmacokinetic assessment subcohort, a 12-week open-label lead-in period, and an up to 32-week placebo-controlled double-blind withdrawal period (figure 1). Patients who completed the 2-week safety and pharmacokinetic assessment proceeded to the open-label lead-in period for 10 weeks. Once a dose was confirmed for an age group in the pharmacokinetic and safety period, new patients in that age group were enrolled directly into the 12-week open-label lead-in period.

The trial was conducted in accordance with the Guidelines for Good Clinical Practice, the Declaration of Helsinki, and local regulatory requirements and laws. Approval was obtained by institutional review boards or ethics committees from all participating sites (per country and sites) according to local requirements. 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 (pp 40–269). Eligible patients who participated in JUVE-BASIS were offered enrolment into a 264-week open-label extension study of baricitinib (NCT03773965), to evaluate long-term safety and tolerability in the selected patient population.

Participants

In response to a paediatric investigation plan agreed with the European Medicines Agency and recommended by clinical experts, eligible patients were children and adolescents (age 2 to <18 years) with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis [positive or negative for rheumatoid factor; RF], extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or juvenile psoriatic arthritis), as per the ILAR criteria,[18] with an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs. Patients must have been treated for at least 12 weeks any time prior to screening before an assessment of inadequate response per study investigator's judgement. At screening and baseline, the eligibility requirement was for patients with polyarticular or extended oligoarticular juvenile idiopathic arthritis to have at least five active joints; for those with juvenile psoriatic arthritis to have at least three active joints; and for those with enthesitis-related arthritis to have at least three active joints, or active arthritis in at least one sacroiliac joint plus a physician global assessment score of at least 3 (with a score of 0 defined as inactive juvenile idiopathic arthritis, and 10 defined as very active juvenile idiopathic arthritis on a visual analogue scale).[19] Baseline was defined as the last non-missing study assessment recorded on or before the date of first study drug administration. Active joints were defined as those with joint swelling or, in the absence of swelling, limitation of motion plus pain on motion or tenderness on palpation.[17]

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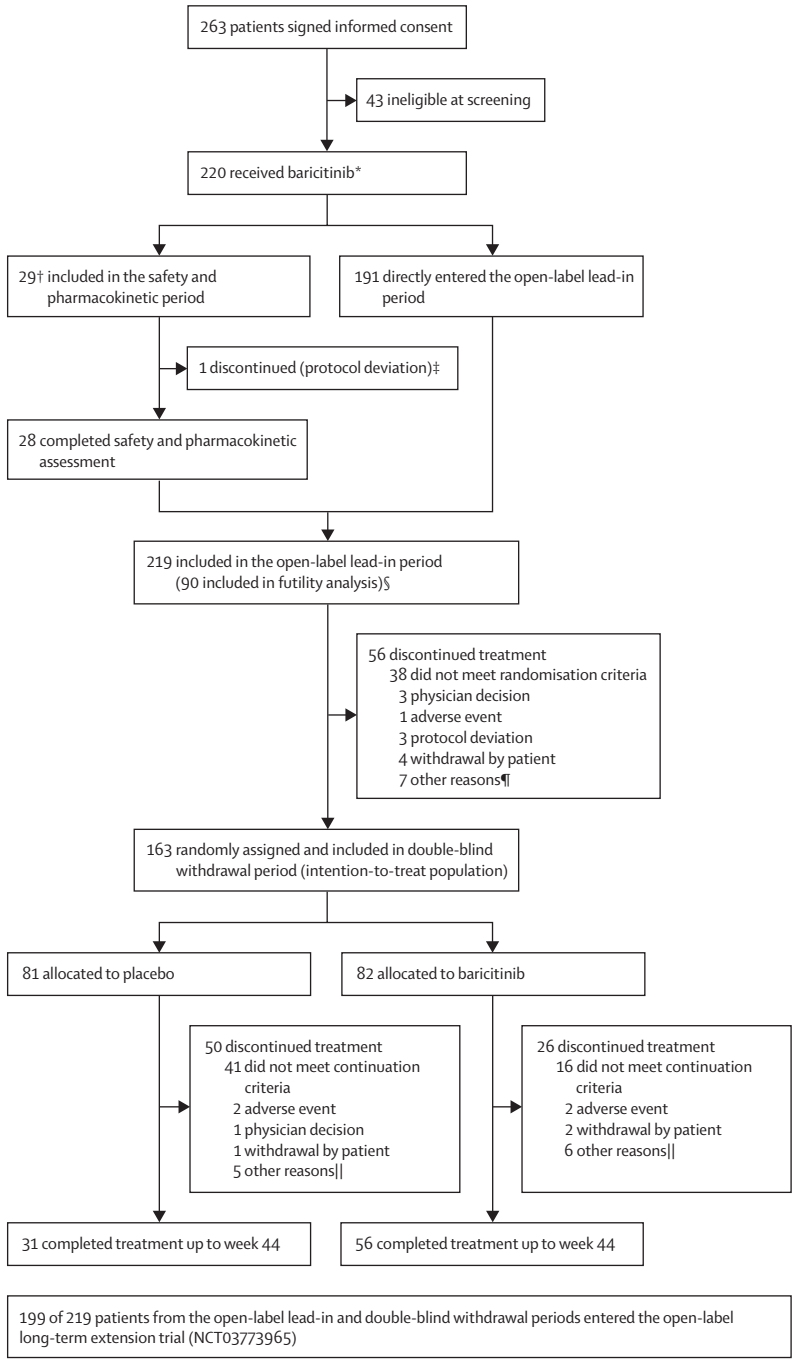

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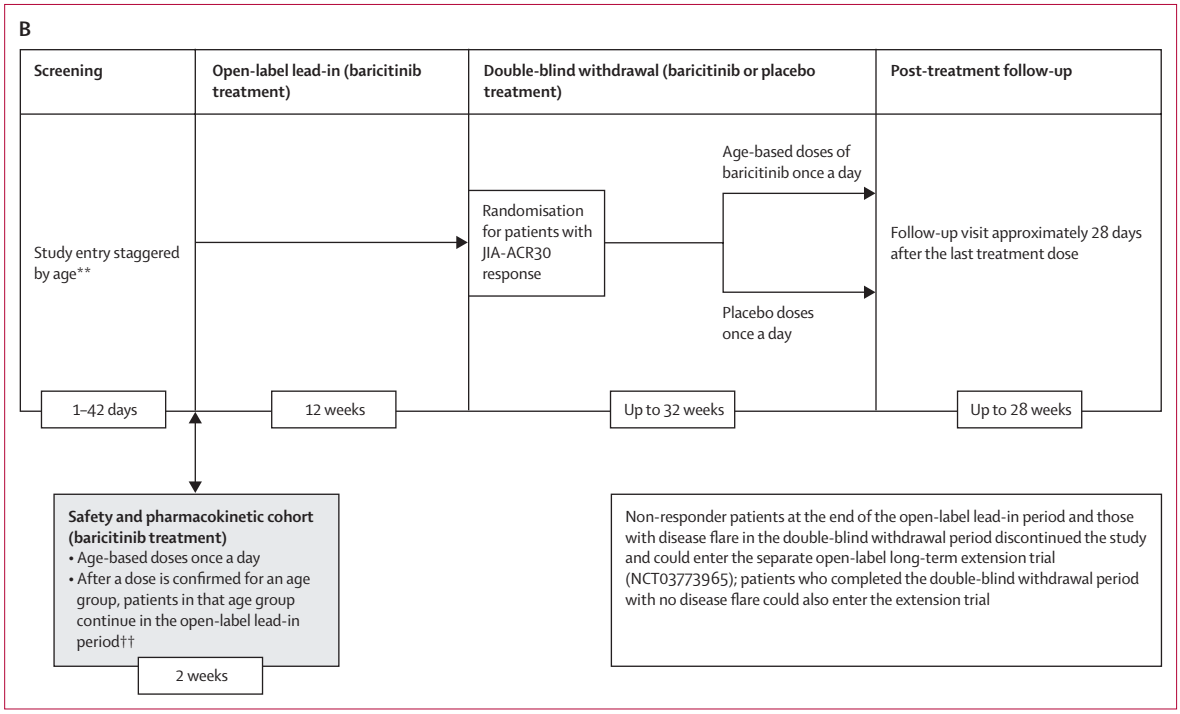

Figure 1: **Trial profile (A) and study design (B)**
Non-responder was defined as absence of at least a JIA-ACR30 response. JIA-ACR30=Juvenile Idiopathic Arthritis-American College of Rheumatology 30 criteria. Footnotes for part A: *Safety was determined in all patients who received at least one dose of baricitinib throughout the trial (n=220). †29 eligible of 57 screened; these patients completed the safety and pharmacokinetic assessment period before the corresponding age groups entered directly into the open-label lead-in period. ‡Not an appropriate enrolment due to untreated latent tuberculosis. §67 (74%) of 90 patients had a JIA-ACR30 response (the study was to be stopped for futility if less than 50% of the first 100 patients to complete the open-label lead-in period had a JIA-ACR30 response). ¶Five patients discontinued due to the COVID-19 pandemic, one due to a required intra-articular corticosteroid injection that was not permitted during the study, and one patient due to absence of materials on site. ||Ten patients discontinued due to the COVID-19 pandemic, and one patient who received baricitinib was discontinued after a study team decision due to the patient being a non-responder at week 12. Footnotes for part B: **Staggered approach to enrolment by age group (12–17 years, 9–11 years, 6–8 years, and 2–5 years) was implemented with older groups completing the safety and pharmacokinetic assessment period before younger groups were enrolled. ††Once the safety and pharmacokinetic profiles for an age group were established, subsequent patients in that age group were enrolled directly into the open-label lead-in period.

Excluded patients were those with systemic juvenile idiopathic arthritis, persistent oligoarticular juvenile idiopathic arthritis (both as defined by ILAR criteria[18]), anterior uveitis (active or receiving concurrent treatment for anterior uveitis), or current or recent (<4 weeks before baseline) clinically serious infection that posed unacceptable risk in the opinion of the investigator, or a history or presence of any autoimmune inflammatory condition such as Crohn's disease or ulcerative colitis. Patient sex was recorded by study investigators at baseline.

Permitted stable background therapies alongside study treatment were glucocorticoids (≤10 mg/day or ≤0·2 mg/kg per day prednisone equivalent, whichever is lower; stable for ≥2 weeks before screening and ≥6 weeks before baseline) and nonsteroidal anti-inflammatory drugs (stable for 1 week before baseline), and up to two conventional synthetic DMARDs (non-methotrexate therapies required to be stable for ≥4 weeks before screening; methotrexate treatment required to be stable for ≥8 weeks before screening at an average dose of ≤20 mg/m² per week to account for schedule variability). Background therapies remained unchanged throughout the study, unless dose adjustment of conventional synthetic DMARDS was required for safety reasons. Notably, appropriate washout of previous biologic DMARDs was required (ie, ≥4 weeks before screening for TNF, IL-1, and IL-6 inhibitors, or abatacept; and ≥6 months for rituximab). There were no limits on the number of previous biologic DMARDs used for juvenile idiopathic arthritis. Additional inclusion and exclusion criteria and prohibited medications are included in the protocol (appendix pp 81–90). Written informed consent or assent, when appropriate, was provided by parents, legal guardians, or patients.

Randomisation and masking

Patients were randomly assigned (1:1) to receive placebo or baricitinib in the double-blind withdrawal period. Randomisation was done via a computer-generated random sequence from an interactive web-response system, stratified by history of previous biologic DMARD use, juvenile idiopathic arthritis category (polyarticular

juvenile idiopathic arthritis and extended oligoarticular juvenile idiopathic arthritis combined *vs* enthesitis-related arthritis and juvenile psoriatic arthritis combined), and, for patients with polyarticular juvenile idiopathic arthritis, predose-exposure erythrocyte sedimentation rate category (elevated [>20 mm/h] *vs* not elevated). Randomisation was performed by a dedicated interactive web-response system team at Eli Lilly and Company, who provided support for the computer system. Access was provided on any computer through a secured web portal. Masked site personnel confirmed that they had the correct packages containing placebo or baricitinib by entering a confirmation number found on the packages into the interactive web-response system before dispensing to the patient. Patients, investigators, the Eli Lilly team, an independent external clinical event committee (Cleveland Clinic Coordinating Center for Clinical Research; Cleveland, OH, USA), and any personnel interacting directly with patients or sites were masked to treatment assignment. An external independent data monitoring committee was unmasked to treatment allocation. A dual assessor approach was used to avoid potential unmasking, which involved a joint assessor and physician assessor.[15] Placebo tablets and oral suspension were developed to match those of the investigational products.

Procedures

The 2-week safety and pharmacokinetic period was designed to confirm the appropriateness of the baricitinib dosing regimen in children, with the aim of establishing an exposure of baricitinib in children that reflected a once daily 4 mg adult-equivalent dose (appendix pp 17–18). Enrolment for the safety and pharmacokinetic period was staggered so that the 2-week assessment period in older groups of patients was completed before younger groups were enrolled. The age groups in order of enrolment were 12–17 years, 9–11 years, 6–8 years, and 2–5 years, with five to eight patients per age group. Sample sizes were empirical and not formally powered. Age-based doses were administered once a day. Whole blood samples were collected from all patients on days 1, 4, and 14, and baricitinib plasma concentration data were overlayed on actual and predicted concentration values which were calculated from samples from previous trials of baricitinib in adults (aged ≥18 years) with rheumatoid arthritis.[20] Concentration data from the safety and pharmacokinetic period and also from the open-label lead-in period (blood samples taken at each weekly visit up to week 12) were included in a post-hoc population pharmacokinetic model, with parameters described in detail in the appendix (pp 17–18, 25). All patients younger than 6 years received oral suspension, patients aged 6 to 11 years could choose (with caregiver consent) between oral suspension or tablets, while patients aged 12–17 years were supplied tablets only. The oral suspension was coloured white and flavoured orange. Suspension acceptability and palatability was assessed via questionnaire, in which patients' views relating to the taste and smell of the suspension and ease of administering and receiving the suspension were recorded. The questionnaire was designed internally, by the pharmaceutical product design group at Eli Lilly and Company, for trials in the juvenile population on the basis of previous literature.[21,22] The questionnaire was completed by parents for children aged 2–7 years or was self-completed for children aged 8 years or older, and was administered after approximately 12–14 weeks of treatment. After a baricitinib dose was confirmed for an age group in the 2-week pharmacokinetic assessment period, patients in that age group continued treatment for 10 weeks in the open-label lead-in period. After confirmation of age-based dose, subsequently enrolled patients in that age group were enrolled directly into the 12-week open-label lead-in period (figure 1).

At the end of the open-label lead-in period (week 12 from baseline), patients who did not have at least a Juvenile Idiopathic Arthritis-American College of Rheumatology (JIA-ACR) 30 response (JIA-ACR30; ie, ≥30% improvement in at least three of six JIA-ACR core response variables without ≥30% worsening in more than one of the remaining core response variables)[23] were classed as being non-responsive to baricitinib, and were discontinued from the study and offered enrolment into the long-term extension study. The JIA-ACR core response variables[23] are physician's global assessment of disease activity, parent's global assessment of patient's overall wellbeing (included in the Childhood Health Assessment Questionnaire [CHAQ]-Discomfort Index[24]), number of joints with active arthritis, number of joints with limitation of motion, validated translation of CHAQ-Disability Index[24] (to assess the core response variable of functional ability), and erythrocyte sedimentation rate. The CHAQ Disability Index and Discomfort Index were completed by parents or legal guardians regardless of patient age.

Patients with a JIA-ACR30 response or better at the end of the open-label lead-in period were eligible to proceed to the double-blind withdrawal period and were randomly assigned (1:1) to receive placebo or continue receiving age-based doses of baricitinib for up to 32 weeks or until the occurrence of a disease flare, defined as worsening of at least 30% in at least three of the six core response variables without improvement of at least 30% in more than one of the remaining core response variables, compared with week 12.[25] Arthritis flare as an indicator of disease worsening is an established endpoint in open-label and double-blind study designs for juvenile idiopathic arthritis.[17] On completion of a patient's last visit in the double-blind withdrawal period, the patient could enter the open-label long-term extension study (regardless of the occurrence of disease flare) after obtaining patient and caregiver consent.

On-site electronic clinical outcome assessments were used to record all core response variable measurements.

Core response variable measurements were performed at weeks 2, 4, 8, and 12 during the open-label lead-in period and every 4 weeks from weeks 16 to 44, inclusive, during the double-blind withdrawal period. JIA-ACR response and flare events were calculated independently by the sponsor, and communicated to the investigator in real-time (while the patient was still at the study site). Other assessments included Juvenile Arthritis Disease Activity Score 27 joints (JADAS-27),[26] HQoL measured with the validated Child Health Questionnaire–Parent Form 50 (CHQ-PF50),[24] and patient or parent assessment of child's pain via the CHAQ pain severity scale (0–100 mm visual analogue scale) to assess the level of pain severity in the past week (where 0 was defined as no pain and 100 was defined as very severe pain).

Adverse events were assessed at all study visits from baseline to the final visit by the site investigator. Adverse events and serious adverse events, temporary interruption, and permanent discontinuation of investigational product were defined as per the Medical Dictionary for Regulatory Activities (version 24.1) and results from laboratory tests graded according to the Common Terminology Criteria for Adverse Events (version 5.0). Treatment-emergent adverse events were defined as adverse events that first occurred or worsened in severity on or after the date of the first dose of study treatment (appendix p 126). All adverse events occurring after obtaining appropriate consent for study inclusion were recorded and assessed for serious criteria (appendix p 112). Patients with multiple occurrences of the same event were counted once for the occurrence of highest severity. Investigators interpreted and documented whether adverse events had reasonable possibility of being related to study treatment. The severity of adverse events (mild, moderate, and severe) was determined on the basis of medical judgement by the respective investigators and no independent adjudication of adverse event severity occurred. A list of adverse events of special interest is included in the appendix (p 113). The full schedule of follow-up assessments is provided in the protocol (appendix pp 48–62).

A major protocol amendment was made in 2020, when baseline assessment of sexual maturity, additional measurements for height, and imaging procedures were included or increased in frequency for additional growth monitoring (appendix p 117). Dosing was also updated per protocol requirements after pharmacokinetic analysis (appendix p 77), and other minor changes included the addition of provisional language for participation in the study during exceptional circumstances such as the COVID-19 pandemic. A section on mitigations due to COVID-19 is included in the appendix (p 15).

Outcomes

The primary endpoint was time to disease flare during the double-blind withdrawal period. Key secondary endpoints included the proportion of patients with a disease flare during the double-blind withdrawal period, JIA-ACR30, JIA-ACR50, JIA-ACR70, JIA-ACR90, JIA-ACR100, and JIA-ACR inactive disease responses[23,27] in the open-label and double-blind periods, and changes from baseline throughout the open-label and double-blind periods in each of the core response variables.

Other efficacy secondary endpoints assessed at each visit included change from baseline in the Juvenile Arthritis Disease Activity Score 27 joints (JADAS-27),[26] and the proportions of patients with minimal disease activity (as defined previously[26,28]). Change from baseline in HQoL was assessed via the CHQ-PF50 Physical and Psychosocial Summary scores, for which a change in score of 10 is considered clinically relevant.[24] Additionally, change from baseline in CHAQ pain severity score (visual analogue scale) was assessed. A post-hoc analysis was done to calculate JADAS-27 over time. A change in JADAS-27 greater than 5·5 is considered a clinically meaningful difference.[29]

Safety endpoints included adverse events and serious adverse events, and temporary interruptions and permanent discontinuations of investigational product, for the duration of the trial.

Statistical analysis

The clinical trial report followed the CONSORT 2010 statement.[30] Assuming a 65% JIA-ACR30 response rate during the open-label lead-in period, a two-sided test with a significance level of 0·05, and expected percentages of patients with disease flare during the double-blind withdrawal period of 35% in the baricitinib group[15,31] and 60% in the placebo group,[32] a minimum of 197 patients were needed to provide a power of at least 80% to detect the difference in time to disease flare between the baricitinib and placebo groups. The analysis followed the intention-to-treat principle for all primary and all secondary efficacy analyses in the double-blind withdrawal period (ie, patient data were reported within the group to which they were randomly assigned, regardless of any potentially confounding circumstances). For the open-label lead-in period, the population assessed was all participants who took at least one dose of the final age-based dose, as confirmed by pharmacokinetic assessments of investigational product, in the open-label lead-in period. This population excluded one patient who received a dose during the safety and pharmacokinetic phase but did not enter the open-label lead-in period (figure 1).

The primary outcome of time to disease flare (in weeks) during the double-blind withdrawal period was calculated with the Kaplan-Meier method and a log-rank test stratified by juvenile idiopathic arthritis categories (polyarticular juvenile idiopathic arthritis and extended oligoarticular juvenile idiopathic arthritis combined *vs* enthesitis-related arthritis and juvenile psoriatic arthritis combined) was used to detect the difference between treatment groups. Hazard ratios (HRs) and 95% CIs were calculated with a Cox proportional hazard regression

model adjusted for juvenile idiopathic arthritis categories (polyarticular and extended oligoarticular types *vs* enthesitis-related arthritis and juvenile psoriatic arthritis), predose-exposure erythrocyte sedimentation rate (elevated [>20 mm/h] *vs* not elevated), and history of previous biologic disease-modifying antirheumatic drug use (yes *vs* no). Time to disease flare, with associated HRs and 95% CIs, was also calculated for subgroups (gender, age group, geographical region, juvenile idiopathic arthritis category, predose-exposure erythrocyte sedimentation rate, history of previous biologic DMARD use, and methotrexate use at baseline) with a Cox proportional hazard regression model adjusted for the same covariates as for the primary analysis. Logistic regression was used to analyse categorical secondary endpoints, and ANCOVA models for continuous secondary endpoints. Statistical tests of treatment effects and 95% CIs were computed at a two-sided significance level of 0·05. Patients who discontinued or completed the double-blind withdrawal period without having a flare had their data censored at the time of their discontinuation date or completion date, respectively. The censored patients contributed to the at-risk set in the stratified log-rank test in the primary endpoint analysis. All missing continuous endpoints were imputed with the last observation carried forward (LOCF) method after applying the censoring rule for patients who discontinued study drug (ie, efficacy and health outcome data collected after permanent study drug discontinuation were excluded from the analyses). For categorical endpoints, if the endpoint was derived on the basis of continuous components and at least one continuous component was not missing, the LOCF was applied to impute the missing component within a treatment period; otherwise non-responder imputation was applied to impute missing data. In the double-blind withdrawal period, ANCOVA was used as the main analysis for all continuous efficacy and health outcomes variables. Type 3 sums of squares for the least-squares mean were used for the statistical comparison of treatment groups, and the least-squares mean with standard error and least-squares mean difference with 95% CIs are reported. Secondary efficacy endpoints were not controlled for multiplicity; thus, only nominal p-values are provided.

Safety was assessed in all patients who received at least one dose of baricitinib throughout the trial. The primary safety analysis was conducted for the safety population in the double-blind withdrawal period. For adverse events occurring in the double-blind withdrawal period, incidence rates (IRs; exposure-adjusted incidence rate per 100 patient-years of exposure) are reported. Fisher's exact test was used for between-group comparisons of adverse events, discontinuations, and other categorical (laboratory) safety data; all values were non-significant (p>0·05) and are not reported herein. The 95% CIs for odds ratio were based on normal approximation (not reported herein) and 95% CIs for IRs were based on Poisson approximation. Potential major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke), other cardiovascular events (such as hospitalisation for unstable angina, hospitalisation for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, and coronary interventions), arterial thromboembolic events, venous thrombotic events, and non-cardiovascular deaths were identified by the site investigator or through masked medical review by the clinical event committee and were adjudicated by the masked clinical event committee at regular intervals. PRINTO did an independent evaluation of the primary and secondary endpoints in a subset of 217 patients (those with available data at the time of evaluation), to ensure alignment with the electronic clinical outcome assessments algorithm, with all discrepancies resolved by consensus among individuals from PRINTO and Eli Lilly and Company. In addition, a futility analysis was done to assess the JIA-ACR30 response rate observed in the first 100 patients who completed the open-label lead-in phase. The study was to be stopped for futility if less than 50% of the first 100 patients to complete the open-label lead-in period had a JIA-ACR30 response.

The sponsor used an external data monitoring committee, consisting of paediatric experts, biostatisticians, and paediatric endocrinologists with expertise in growth and development, to evaluate planned interim analyses. The data monitoring committee reviewed adverse events (treatment-emergent and serious adverse events, and adverse events of special interest), among others listings and summaries. Reviews by the data monitoring committee were conducted twice a year during the study (from the first patient visit up to the last patient visit and final safety data). Additionally, the data monitoring committee met to review the safety and pharmacokinetic datasets to agree on appropriate dosing and proceed with the next youngest age group, and met to conduct the futility analysis after 100 patients completed the open-label lead-in period. The data monitoring committee evaluated all aggregate data (including unmasked data from the double blind withdrawal period) that included demographics, efficacy outcomes (during the open-label lead-in and double-blind withdrawal period), laboratory tests, vital signs, and growth measures. The data monitoring committee did not recommend changes to the conduct of the study in any of the data monitoring committee meetings.

Data were managed in InForm Electronic Data Capture (version 6.2), and statistical analyses were done with SAS (version 9.4). The trial was registered with ClinicalTrials.gov, NCT03773978, and is completed.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

	Safety and pharmacokinetic and open-label lead-in period (baricitinib treatment, n=220)	Double-blind withdrawal period	
		Placebo (n=81)	Baricitinib (n=82)
Age at enrolment, years	14·0 (12·0–16·0)	14·0 (12·0–16·0)	14·0 (12·0–16·0)
Age at diagnosis, years	10·0 (6·0–13·0)	9·0 (5·0–13·0)	11·0 (7·0–13·0)
Time since juvenile idiopathic arthritis diagnosis, years	2·7 (1·0–6·0)	3·1 (2·0–6·0)	2·0 (1·0–5·0)
Sex			
Female	152 (69%)	59 (73%)	56 (68%)
Male	68 (31%)	22 (27%)	26 (32%)
Weight, kg	50·5 (39·1–61·0)	51·8 (40·0–63·0)	50·6 (38·5–59·6)
Race	n=214*	n=80*	n=80*
Asian	48 (22%)	12 (15%)	22 (28%)
White	152 (71%)	62 (78%)	56 (70%)
Other	14 (7%)	6 (8%)	2 (3%)
Geographical region			
Asia	75 (34%)	22 (27%)	34 (41%)
South America	22 (10%)	8 (10%)	10 (12%)
Europe	101 (46%)	47 (58%)	29 (35%)
Rest of the world	22 (10%)	4 (5%)	9 (11%)
Age categories, years			
2–5	6 (3%)	1 (1%)	5 (6%)
6–8	9 (4%)	5 (6%)	3 (4%)
9–11	30 (14%)	9 (11%)	9 (11%)
12–17	175 (80%)	66 (81%)	65 (79%)
Juvenile idiopathic arthritis clinical characteristics			
Type of juvenile idiopathic arthritis			
Polyarticular juvenile idiopathic arthritis	144 (66%)	51 (63%)	57 (70%)
Extended oligoarticular juvenile idiopathic arthritis	16 (7%)	7 (9%)	5 (6%)
Enthesitis-related juvenile idiopathic arthritis	50 (23%)	20 (25%)	16 (20%)
Juvenile psoriatic arthritis	10 (5%)	3 (4%)	4 (5%)
Previous or concurrent therapy†			
Concurrent methotrexate therapy‡	127 (58%)	42 (52%)	55 (67%)
Previous conventional synthetic DMARD therapy	220 (100%)	81 (100%)	82 (100%)
Previous biologic DMARD therapy	116 (53%)	42 (52%)	33 (40%)
Predose-exposure erythrocyte sedimentation rate category	n=217*	n=81	n=80*
Elevated (>20 mm/h)	100 (46%)	37 (46%)	36 (45%)
Not elevated (≤20 mm/h)	117 (54%)	44 (54%)	44 (55%)

Data are median (IQR) or n (%). Baseline was defined as the last non-missing study assessment recorded on or before the date of first study drug administration. DMARD=disease-modifying antirheumatic drug. *Number of patients with available data. †Of the total 220 patients, 72 (33%) were receiving concomitant oral corticosteroids and 40 (18%) were receiving concomitant conventional synthetic DMARDs other than methotrexate (sulfasalazine [n=27], leflunomide [n=5], hydroxychloroquine [n=5], ciclosporin [n=3], and azathioprine [n=1]); patients could receive up to two conventional synthetic DMARDs during the trial per protocol. ‡Concurrent treatment with methotrexate limited to a stable dose (average dose of ≤20 mg/m² per week).

Table 1: **Baseline demographic characteristics**

Results

Study enrolment occurred between Dec 17, 2018, and March 3, 2021. 220 patients were eligible and enrolled in the trial, and received at least one dose of baricitinib. Of these patients, 29 (13%) participated in the safety and pharmacokinetic period, and 219 (>99%) received baricitinib in the open-label lead-in period. One patient was discontinued from the safety and pharmacokinetic period due to having untreated latent tuberculosis as defined in the protocol.

Plasma concentration–time data were used to confirm exposure-matching in patients with juvenile idiopathic arthritis to the exposure observed in adult patients with rheumatoid arthritis receiving 4 mg baricitinib once a day. We presented the individual observed plasma concentrations of baricitinib for all age groups receiving baricitinib 2 mg or 4 mg once a day during the pharmacokinetic and safety period, and the mean (95% CI) and observed plasma concentration of baricitinib in adult patients with rheumatoid arthritis receiving baricitinib 4 mg once a day (ie, the anticipated efficacious exposure level; appendix pp 17–18). The observed concentration data from paediatric patients aged 9–11 years and 12–17 years receiving 4 mg baricitinib once a day, and from paediatric patients aged 2–5 years and 6–8 years receiving 2 mg baricitinib once a day, were overall consistent with the baricitinib exposure in adult patients with rheumatoid arthritis receiving 4 mg once a day. Exposure estimates from the post-hoc population pharmacokinetic analysis (area under the curve and maximum concentration of drug in the body) were overall consistent with those for adult patients (appendix p 25).

At the end of the open-label lead-in period (week 12), 163 (74%) of 219 patients had at least a JIA-ACR30 response and were eligible for random assignment in the double-blind withdrawal period, in which 82 (37%) of 219 were assigned to baricitinib and 81 (37%) to placebo (figure 1). The open-label long-term extension study enrolled 199 (91%) of 219 patients. A listing of patients by country is included in the appendix (p 26). The most common reasons for study discontinuation were absence of at least a JIA-ACR30 treatment response in the open-label lead-in period and disease flare in the double-blind withdrawal period.

Baseline demographics and disease characteristics of all study patients, in the safety and pharmacokinetic and open-label lead-in periods (combined; n=220) and in the randomised groups in the double-blind withdrawal period (n=163), are shown in tables 1 and 2. Baseline demographics for patients who did not continue into the double-blind withdrawal period, and for those who continued into the double-blind withdrawal period (combined treatment groups), are presented in the appendix (pp 27–28). The overall study population comprised 152 (69%) girls and 68 (31%) boys, and median age was 14·0 years (IQR 12·0–16·0). Patient demographics

were well balanced after randomisation in the double-blind withdrawal period (table 1). Mean CHAQ scores were greater than 0·63 at baseline (table 2), meeting the threshold for mild-to-moderate disability.[33] Overall, 116 (53%) of 220 patients had previous biologic DMARD exposure (mainly to TNF inhibitors, n=113), and 127 (58%) were receiving methotrexate during the study, with all patients having a history of methotrexate use since disease onset (table 1).

In the cohort included in the futility analysis, a JIA-ACR30 response was observed with baricitinib treatment in 67 (74%) of 90 patients at week 12. These data were provided to the data monitoring committee who concluded that futility criteria were not met, and the study should proceed without modification. In the open-label lead-in period, 56 (26%) of 219 patients discontinued treatment, of whom 38 (17%) were non-responders (ie, did not meet JIA-ACR30 criteria) at the end of the period (week 12), 14 (6%) discontinued for other reasons, and four (2%) patients withdrew from the trial despite having a JIA-ACR30 response at the end of the period (figure 1).

	Open-label lead-in period (baricitinib treatment, n=219)		Double-blind withdrawal period			
	Baseline	Change from baseline at week 12	Baseline		Change from baseline at week 44 (least-squares mean) and least-squares mean difference *vs* placebo	
			Placebo (n=81)	Baricitinib (n=82)	Placebo (n=81)	Baricitinib (n=82)
Disease flare						
Proportion with flare*	..	..	..	..	41 (51%; 40 to 62)	14 (17%; 9 to 25), p<0·0001
Time to flare*	..	..	..	..	..	0·241 (0·128 to 0·453), p<0·0001
JIA-ACR core response variables						
Number of joints with active arthritis†	12·8 (11·1)	–8·02 (0·422); n_o=206	10·9 (8·4)	13·0 (9·5)	–6·19 (0·715); n_{LOCF}=79, n_o=33	–10·04 (0·720); n_o=55; difference *vs* placebo –3·85 (–5·71 to –1·99), p<0·001
Number of joints with limited range of motion‡	8·8 (9·6); n_{LOCF}=217	–4·36 (0·379); n_o=206	8·3 (9·1)	8·8 (8·0)	–2·93 (0·679); n_{LOCF}=79, n_o=33	–6·34 (0·694); n_o=55; difference *vs* placebo –3·41 (–5·19 to –1·63), p<0·001
Physician's global assessment of disease activity score§	6·5 (2·0)	–3·72 (0·161); n_o=208	6·3 (1·9)	6·6 (1·8)	–2·96 (0·318); n_{LOCF}=79, n_o=33	–4·32 (0·322); n_o=55; difference *vs* placebo –1·36 (–2·19 to –0·53), p=0·002
Parent's global assessment of patient's overall wellbeing score¶	53·6 (25·0); n_{LOCF}=217	–24·42 (1·625); n_{LOCF}=215, n_o=207	53·2 (24·8)	55·6 (24·4)	–18·94 (3·207); n_{LOCF}=79, n_o=32	–29·43 (3·276); n_o=55; difference *vs* placebo –10·50 (–18·93 to –2·06), p=0·015
Disability index as measured by the Childhood Health Assessment Questionnaire‖	1·2 (0·7); n_{LOCF}=217	–0·46 (0·037); n_o=207	1·2 (0·7)	1·2 (0·7)	–0·38 (0·072); n_{LOCF}=79, n_o=32	–0·66 (0·074); n_o=55; difference *vs* placebo –0·28 (–0·47 to –0·09), p=0·004
Erythrocyte sedimentation rate, mm/h**	27·3 (24·6); n_{LOCF}=216	–8·39 (1·133); n_{LOCF}=214, n_o=206	25·9 (24·3)	26·4 (21·2)	–6·57 (2·133); n_{LOCF}=78, n_o=33	–8·99 (2·188); n_{LOCF}=80, n_o=54; difference *vs* placebo –2·42 (–8·04 to 3·20), p=0·40
Disease activity						
Juvenile Arthritis Disease Activity Score 27	21·7 (8·8); n_{LOCF}=214	-12·37 (0·500); n_o=203	20·3 (8·6)	22·5 (8·0)	–9·91 (1·013); n_{LOCF}=78, n_o=33	–14·24 (1·006); n_{LOCF}=80, n_o=54; difference *vs* placebo –4·33 (–6·95 to –1·70), p=0·001

Values at baseline are reported as mean (SD). Change from baseline was computed from LOCF analysis and is reported as the least-squares mean (SE) and the least-squares mean difference (95% CI) *vs* placebo (week 44), unless otherwise indicated. p values are for baricitinib versus placebo and are nominal except for the primary endpoint (time to flare). In cells where n_{LOCF} and n_o are not provided, the total population of the respective group (open-label lead-in period n=219, double-blind placebo group n=81, or double-blind baricitinib group n=82) was analysed for the measure. The open-label lead-in population comprised all patients who took at least one age-based final dose, as confirmed by pharmacokinetic assessments of investigational product, in the open-label lead-in period, not including one patient who discontinued in the safety and pharmacokinetic period. The double-blind withdrawal population comprised all randomly assigned patients following intention-to-treat principles. JIA-ACR=Juvenile Idiopathic Arthritis-American College of Rheumatology criteria. n_{LOCF}=number of patients in the LOCF analysis population. n_o=number of patients with an observed value. LOCF=last observation carried forward. *Proportion with flare presented as n (%; 95% CI) for patients who presented with flare during the double-blind withdrawal period; time to flare reported as hazard ratio (95% CI) for baricitinib versus placebo. †Out of 73 joints assessed. ‡Out of 69 joints assessed. §Range from 0–10 (higher value indicating maximum activity). ¶Range from 0–100 mm on a visual analogue scale (higher value indicating worse wellbeing). ‖Range from 0 to 3 (0, no disability, to 3, very severe disability). **Elevated rate defined as >20 mm/h.

Table 2: **Primary and secondary efficacy endpoints at baseline and changes from baseline in the open-label lead-in and double-blind withdrawal periods**

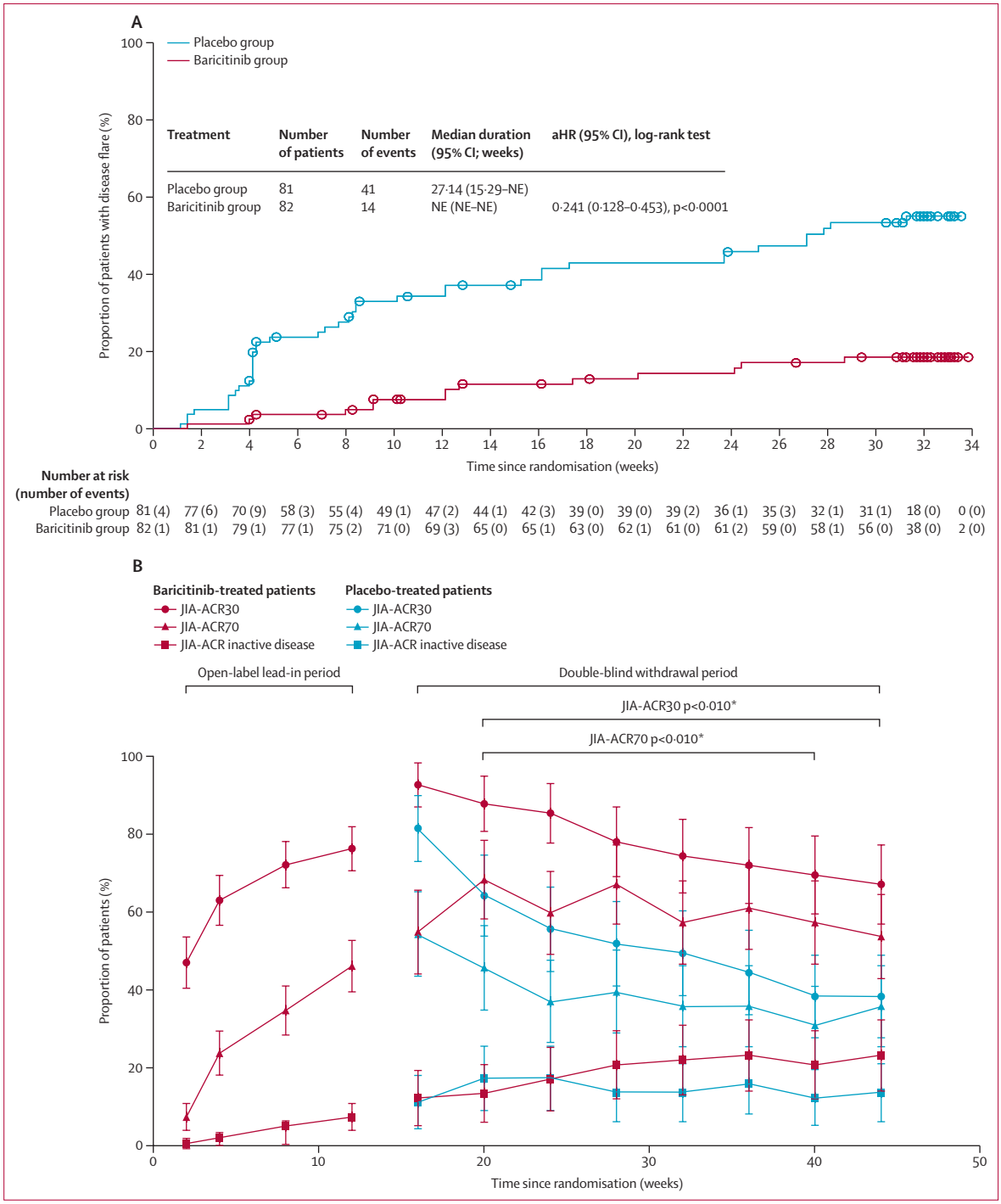

Figure 2: **Efficacy of baricitinib versus placebo for time to flare and JIA-ACR response**

A) Kaplan-Meier plot of time to flare with baricitinib treatment versus placebo during the double-blind withdrawal period (n=163). Circles represent patients who discontinued or completed the double-blind withdrawal period without experiencing a flare and had their data censored at the time of their discontinuation or completion date. B) JIA-ACR30, JIA-ACR70, and JIA-ACR inactive disease[27] response rates with 95% CIs during the open-label lead-in period (n=219) and double-blind withdrawal period (n=163). Source data are provided in the appendix (appendix pp 29–31). JIA-ACR=Juvenile Idiopathic Arthritis-American College of Rheumatology response level. aHR=adjusted hazard ratio. NE=not estimable. *Nominal p value for baricitinib versus placebo treatment at the indicated JIA-ACR response level.

At the end of the open-label lead-in period, 167 (76%) patients had a JIA-ACR30 response, 101 (46%) had a JIA-ACR70 response, and 16 (7%) had JIA-ACR inactive disease (figure 2B; appendix p 29). Mean JADAS-27 decreased by 6·91 (SE 0·43) at week 2 of the open-label lead-in period, and by 12·37 (0·50) at the

end of the open-label lead-in period, compared with baseline. All core response variables showed improvements from baseline to the end of the open-label lead-in period (table 2; appendix p 34).

The study reached its primary endpoint, with time to juvenile idiopathic arthritis flare being significantly shorter in the placebo group than in the baricitinib group in the double-blind withdrawal period (baricitinib *vs* placebo adjusted HR 0·241 [95% CI 0·128–0·453], p<0·0001; figure 2A). The median time to disease flare was 27·14 weeks (95% CI 15·29–not estimable) for the placebo group and was not evaluable for the baricitinib group as less than 50% of patients assigned to baricitinib had a disease flare during the double-blind withdrawal period. The disease flare rate during the double-blind withdrawal period was significantly lower in the baricitinib group than in the placebo group (14 of 82 patients, 17% [95% CI 9–25] *vs* 41 of 81, 51% [40–62]; p<0·0001; table 2, appendix p 19). In subgroup analyses, results across the subgroups were directionally consistent with the effect observed in the overall population. Notably, a significant treatment effect with baricitinib was indicated in both sex subgroups; in patients aged 12–17 years; in patients from Asia and Europe; in the polyarticular juvenile idiopathic arthritis group, and the polyarticular juvenile idiopathic arthritis and extended oligoarticular juvenile idiopathic arthritis combined group; in patients with or without elevated predose-exposure erythrocyte sedimentation rate; in patients with or without a history of previous biologic DMARD use; and in patients with or without methotrexate use at baseline (appendix p 23). The proportions of patients with disease flare events during the double-blind withdrawal period were numerically lower than what had been assumed during study design (ie, 35% for baricitinib and 60% for placebo). In the baricitinib group, disease flare occurred in ten (18%) of 57 patients with RF-positive or RF-negative polyarticular juvenile idiopathic arthritis; one (20%) of five patients with extended oligoarticular juvenile idiopathic arthritis; three [19%] of 16 patients with enthesitis-related arthritis; and none of four patients with juvenile psoriatic arthritis. In the placebo group, disease flare occurred in 26 (51%) of 51 patients with RF-positive or RF-negative polyarticular juvenile idiopathic arthritis; five (71%) of seven patients with extended oligoarticular juvenile idiopathic arthritis; ten (50%) of 20 patients with enthesitis-related arthritis; and none of three patients with juvenile psoriatic arthritis. Disease flare rates were lower in the baricitinib group versus the placebo group during the double-blind withdrawal period irrespective of methotrexate background use (in patients receiving methotrexate, eight [15%] of 55 *vs* 17 [41%] of 42 had a disease flare; and in patients not receiving methotrexate, six [22%] of 27 *vs* 24 [62%] of 39 had a disease flare).

During the double-blind withdrawal period, JIA-ACR30 and JIA-ACR50 response rates were higher in the baricitinib group versus the placebo group from week 20 up to week 44 since baseline (figures 2B; appendix p 20). The same outcome was observed for JIA-ACR70 response rate from week 20 to week 40 (figure 2B). At week 44 (end of the double-blind withdrawal period) in the baricitinib group (n=82), 55 (67%) patients had a JIA-ACR30 response, 52 (63%) had a JIA-ACR50 response, 44 (54%) had a JIA-ACR70 response, and 19 (23%) had JIA-ACR inactive disease; in the placebo group (n=81), these proportions were 31 (38%), 30 (37%), 29 (36%), and 11 (14%; appendix pp 30–31).

In the open-label lead-in period, there was a reduction in disease activity (JADAS-27) from baseline (mean 21·8 [SD 8·8]) to week 12 (9·4 [8·6]; figure 3). For patients included in the double-blind withdrawal period, mean JADAS-27 at baseline was 22·5 (8·0) in those randomly assigned to baricitinib and 20·3 (8·6) in those randomly assigned to placebo. At week 44, the least-squares mean value for JADAS-27 was 7·2 (95% CI 5·2–9·2) in the baricitinib group and 11·5 (9·5–13·5) in the placebo group. The mean improvement from baseline in the baricitinib group was greater than that in the placebo group from weeks 20 to 44 (appendix p 21). At the end of the open-label lead-in period, 63 (29%) of 219 patients had minimal disease activity (appendix p 32). At the end of the double-blind withdrawal period, the proportions of patients with minimal disease activity was higher in the baricitinib group than in the placebo group.

During the double-blind withdrawal period, both the baricitinib and placebo groups maintained improvements in the core response variables from baseline. At week 44, improvements in five of six core response variables were greater in the baricitinib group versus the placebo group; whereas, improvements in the remaining core response variable (erythrocyte sedimentation rate) was only numerically improved (table 2; appendix pp 35–36).

Patients showed improvements in HQoL on the CHQ-PF50 Physical and Psychosocial summary scales during the open-label lead-in period (appendix pp 22, 32–33).

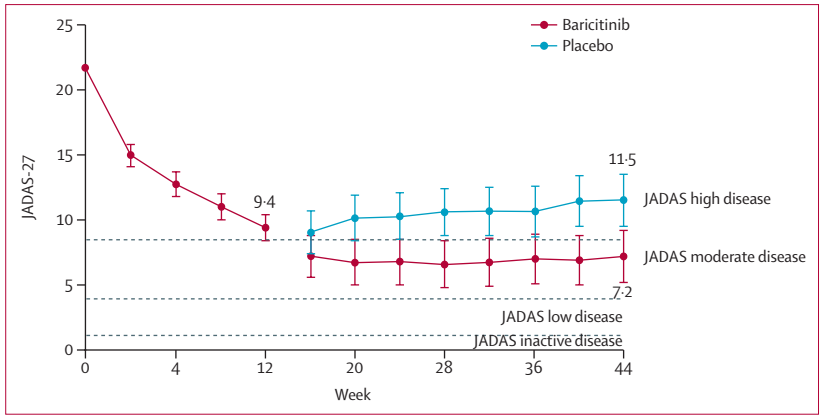

***Figure 3*: JADAS-27 responses in the open-label lead-in period (n=219) and versus placebo in the double-blind withdrawal period (n=163)**

An ANCOVA model was used with treatment and baseline score as covariates, with scores reported as least-squares mean and 95% CIs. JADAS-27 scores can range from 0 to 57 (higher values indicating more severe disease activity). Horizontal dashed lines indicate JADAS-27 disease activity level cutoffs: high (scores >8·5); moderate (scores 3·9–8·5); low (scores 1·1–3·8); and inactive disease (scores ≤1·0).[31] JADAS-27=Juvenile Arthritis Disease Activity Score 27.

	Safety and pharmacokinetic and open-label lead-in periods (baricitinib treatment, n=220)	Double-blind withdrawal period	
		Placebo (n=81, PYE=29·4)	Baricitinib (n=82, PYE=41·4)
Summary of adverse events			
At least one treatment-emergent adverse event	126 (57%)	38 (47%); 214·6 (151·9–294·6)	54 (66%); 254·7 (191·4–332·4)
Severity of treatment-emergent adverse events			
Mild	83 (38%)	24 (30%); 107·1 (68·6–159·4)	31 (38%); 98·2 (66·7–139·4)
Moderate	39 (18%)	12 (15%); 45·4 (23·4–79·3)	21 (26%); 60·8 (37·6–93·0)
Severe	4 (2%)	2 (2%); 6·8 (0·8–24·4)	2 (2%); 4·8 (0·6–17·3)
Serious adverse events*	6 (3%)	3 (4%); 10·2 (2·1– 29·7)	4 (5%); 9·7 (2·7–24·9)
Death	0	0	0
Adverse event* leading to permanent discontinuation of baricitinib or placebo	2 (1%)	2 (2%); 6·8 (0·8–24·4)	1 (1%); 2·4 (0·1–13·3)
Summary of treatment-emergent adverse events occurring in >1% of patients in any group			
Nasopharyngitis	19 (9%)	3 (4%); 10·3 (2·1–30·1)	6 (7%); 15·3 (5·6–33·2)
Upper respiratory tract infection	11 (5%)	1 (1%); 3·4 (0·1–18·8)	9 (11%); 22·9 (10·5–43·5)
Headache	14 (6%)	3 (4%); 10·4 (2·2–30·5)	9 (11%); 23·3 (10·7–44·3)
Arthralgia	12 (5%)	3 (4%); 10·3 (2·1–30·1)	6 (7%); 15·0 (5·5–32·5)
Nausea	11 (5%)	0	3 (4%); 7·4 (1·5–21·5)
Vomiting	10 (5%)	0	1 (1%); 2·4 (0·1–13·3)
Summary of treatment-emergent adverse events of special interest			
Infectious adverse events			
At least one infection	55 (25%)	15 (19%); 59·0 (33·0–97·3)	31 (38%); 102·1 (69·3–144·9)
Serious infection	0	0	2 (2%); 4·9 (0·6–17·5)†
Infections of special interest			
Herpes simplex	1 (<1%)	2 (2%); 6·8 (0·8–24·7)‡	1 (1%); 2·4 (0·1–13·4)
Herpes zoster	1 (<1%)§	0†	0
Infections leading to permanent discontinuation of baricitinib or placebo	0	0	0
Other treatment-emergent adverse events of special interest			
Creatine phosphokinase >5 × ULN§	5/136 (4%)	2/28 (7%)	1/55 (2%)
Haemoglobin decrease (increase to CTCAE grade 4; haemoglobin <6·5 g per dL)	0	0	0
Neutrophil count decrease (increase to CTCAE grade 4; neutrophil count <500 cells per mm^3)	0	0	0

(Table 3 continues on next page)

Additionally, patient pain as measured on the CHAQ pain visual analogue scale markedly improved from baseline to week 12, with continued improvement during the double-blind withdrawal period in the baricitinib group versus the placebo group at week 44 (appendix pp 22, 32–33). Similar effects were seen regarding changes in the CHQ-PF50 Physical Summary score.

Regarding questionnaires on acceptability of the oral suspension, 22 (96%) of 23 patients with completed questionnaires (combined baseline [n=13] and week 12 [n=10]) reported the taste of the medicine to be acceptable and palatable, and 21 (91%) reported the smell of the oral suspension to be acceptable and palatable. 21 (91%) patients reported that it was very easy, easy, or neither easy nor hard to take the oral suspension, and all 21 (100%) caregivers who completed a questionnaire reported that it was very easy or easy to give their child the medicine.

Safety analyses were considered in all 220 patients who received baricitinib. Treatment-emergent adverse events that emerged or worsened (per investigator judgement) in the safety and pharmacokinetic period or open-label lead-in period were reported in 126 (57%) of 220 patients (table 3). In the double-blind withdrawal period, treatment-emergent adverse events occurred in 54 (66%) of 82 patients (IR 254·7 [95% CI 191·4–332·4] per 100 patient-years at risk) in the baricitinib group and 38 (47%) of 81 (IR 214·6 [151·9–294·6]) in the placebo group. Investigators assessed most treatment-emergent adverse events in the three study periods as being mild or moderate in severity. The percentage of patients who discontinued the study due to any adverse events (treatment-emergent or non-treatment-emergent) was low. Serious adverse events were reported in six (3%) of 220 patients in the safety and pharmacokinetic or open-label lead-in period. In the double-blind withdrawal period, serious adverse events were reported in four (5%) of 82 patients (IR 9·7 [2·7–24·9]) in the baricitinib group and three (4%) of 81 (IR 10·2 [2·1–29·7]) in the placebo group. No deaths were reported in the study.

Regarding adverse events of special interest, treatment-emergent infections were reported during the safety and pharmacokinetic or open-label lead-in period in 55 (25%) of 220 patients, and during the double-blind withdrawal period in 31 (38%) of 82 patients (IR 102·1 [95% CI 69·3–144·9] per 100 patient-years at risk) in the baricitinib group and 15 (19%) of 81 patients (IR 59·0 [33·0–97·3]) in the placebo group. During the double-blind withdrawal period, two (2%) patients in the baricitinib group had serious treatment-emergent infections (one patient with COVID-19 and one patient with gastroenteritis), with a corresponding IR of 4·9 (95% CI 0·6–17·5) per 100 patient-years at risk. Additionally, during the safety and pharmacokinetic and open-label lead-in period, one (<1%) patient who received baricitinib reported a treatment-emergent infection that was a mild, non-serious case of herpes zoster infection. In the

double-blind withdrawal period, no herpes zoster infection was reported in the baricitinib group. In the placebo group, two (2%) patients were recorded as having treatment-emergent herpes simplex infection (IR 6·8 [0·8–24·7]); after medical review, one of these cases was determined to be a herpes zoster infection with ocular involvement and two non-contiguous dermatomes.

Other adverse events of special interest including major adverse cardiac events, arterial thromboembolic events, malignancies, gastrointestinal perforations, and tuberculosis infections were not reported in the study. During the double-blind withdrawal period, pulmonary embolism was reported as a serious adverse event in one (1%) patient in the baricitinib group (IR 2·4 [95% CI 0·1–13·3] per 100 patient-years at risk), which was deemed by the investigator to be related to study treatment. The pulmonary embolism was accompanied by associated risk factors (eg, baseline thrombocytosis and overweight, and at the time of the pulmonary embolism event, recent immobilisation, high disease activity, and suspected pneumonia). The pulmonary embolism was confirmed by the external, masked clinical event committee. The diagnosis of suspected pneumonia was based on elevated temperature and radiographic interpretations.

	Safety and pharmacokinetic and open-label lead-in periods (baricitinib treatment, n=220)	Double-blind withdrawal period	
		Placebo (n=81, PYE=29·4)	Baricitinib (n=82, PYE=41·4)
(Continued from previous page)			
Lymphocyte count decrease (increase to CTCAE grade 4; lymphocyte count <50 cells per mm³)	0	0	0
Platelet count increase (thrombocytosis: increase from ≤600 billion cells per L to >600 billion cells per L)¶	5/158 (3%)	1/15 (7%)	1/35 (3%)
Serum alanine aminotransferase ≥3 × ULN¶	5/145 (3%)	0	1/42 (2%)
Serum aspartate aminotransferase ≥3 × ULN¶	3/149 (2%)	0	0
Lipids: low-density lipoprotein cholesterol (≥130 mg/dL)¶	7/110 (6%)	3/32 (9%)	5/43 (12%)
Lipids: triglycerides (age-based high values)‖	6/98 (6%)	9/39 (23%)	5/36 (14%)

Data are number of patients (%) or number of patients (%); IR (95% CI), where IR is the exposure-adjusted incidence rate of the event per 100 patient-years at risk. PYE=patient-years of exposure. CTCAE=Common Terminology Criteria for Adverse Events (version 5.0). ULN=upper limit of normal. IR=incidence rate. *All adverse events occurring after obtaining consent for study inclusion (appendix p 112). †Serious treatment-emergent infections were COVID-19 and gastroenteritis (one patient with each). ‡One patient in the placebo group was reported as having a mild herpes infection of the left eyelid; after medical review, it was considered as potential opportunistic herpes zoster infection with ocular involvement and two non-contiguous dermatomes. §One patient was reported as having herpes zoster; on the basis of medical review the case was not considered an opportunistic infection. ¶Denominators are the number of patients with available data for the specified event in each treatment group. ‖Age-based high values: age 0–9 years, ≥100 mg/dL; age 10–19 years, ≥130 mg/dL.

Table 3: **Summary of adverse events and adverse events of special interest**

Discussion

This clinical trial met its primary endpoint, in that time to juvenile idiopathic arthritis flare was significantly increased in patients receiving baricitinib once a day, compared with those receiving placebo. Furthermore, flare rates were lower in the baricitinib group than in the placebo group, and diverged as early as week 4 of the double-blind withdrawal period. Results showed that, regardless of juvenile idiopathic arthritis categories, flare rates were directionally consistent with those in the overall population. The definition of disease flare used in the study was sensitive, and able to detect subtle changes in disease activity such as those observed in juvenile idiopathic arthritis. This decreased as much as possible the time on placebo in children with juvenile idiopathic arthritis. It is noteworthy that the proportions of patients who had JIA-ACR30 and JIA-ACR50 responses appeared to decrease with time during the double-blind withdrawal period in both the baricitinib and placebo groups, as opposed to the proportion of patients who had a JIA-ACR inactive disease response, which appeared to increase. The subset of patients who had JIA-ACR inactive disease showed more substantial disease control and seemingly were at a lower risk of losing their response status than patients who had a JIA-ACR30 or JIA-ACR50 response during the study.

Baricitinib administration was associated with clinically relevant improvements in validated measures of disease activity. Our findings on the rates of JIA-ACR30 responders and improvement in JADAS-27 with once-daily baricitinib were similar to those in a previous study of JAK inhibition.[15] Indeed, rapid improvement of juvenile idiopathic arthritis activity was observed as early as week 2, and the proportion of JIA-ACR30 responders at the end of the open-label lead in period was similar to that reported previously.[15] Improvements in most secondary endpoints were observed with baricitinib compared with baseline values, irrespective of concurrent methotrexate use. Notably, there were important improvements in patient-reported outcomes, such as pain, physical function, and HQoL. Patient-reported outcomes such as HQoL are increasingly recognised as being more important than measures such as active joint count. Although patients treated with baricitinib showed improvement in pain, physical function, and HQoL, real-world long-term data will provide more relevant evidence. Addressing the burden of juvenile idiopathic arthritis on a patient's HQoL is an important aspect of meaningful treatment.[1]

Although the management of juvenile idiopathic arthritis has been substantially advanced with the approval of biologic DMARDs, a key issue for parents and children is the need for effective non-injectable therapies. JAK inhibitors are a step in this direction. The dosing regimen of baricitinib (once a day) makes

treatment compliance feasible for young patients and their parents or caregivers.[34] The feasibility of oral baricitinib treatment was further indicated in this study by favourable questionnaire responses on acceptability of the baricitinib suspension.

The safety and pharmacokinetic analysis, and population pharmacokinetic analysis, showed that baricitinib exposures in patients aged 2–8 years receiving 2 mg once a day and in those aged 9–17 years receiving 4 mg once a day were similar to exposures in adult patients with rheumatoid arthritis receiving 4 mg once a day. Despite the short pharmacological half-life of baricitinib (around 12 h in the adult population),[35] there were observed delays in juvenile idiopathic arthritis flare events after the discontinuation of baricitinib in the placebo group, whose median time to flare was approximately 190 days. This finding is compatible with a potential residual immunological effect of baricitinib and constitutes clinically relevant information if baricitinib treatment needs to be interrupted, for example if patients with juvenile idiopathic arthritis have infections or undergo elective surgical or medical procedures.

The observed safety profile in patients with juvenile idiopathic arthritis was consistent with the established safety profile in other baricitinib indications in adults,[36] and no new safety signals were identified. The incidence of any infection, in terms of IR per 100 patient-years at risk, was numerically higher in the baricitinib group than in the placebo group in the double-blind withdrawal period. One patient with several risk factors was reported to have pulmonary embolism in the baricitinib group in the double-blind withdrawal period. Although it has been reported that the risk of venous thromboembolism is increased up to two-fold in adult patients with rheumatoid arthritis,[36] the incidence of venous thromboembolism in patients with juvenile idiopathic arthritis, compared with that in the general population, is not well described in the literature. Although no malignancies were reported in this study, long-term studies are needed to provide context for rare events. Nonetheless, the safety profile in juvenile idiopathic arthritis was similar to that reported in other phase 3 trials in juvenile idiopathic arthritis, including for other JAK inhibitors.[7,10,11,15,32,37]

Regarding randomised, blinded, and controlled clinical trials in juvenile idiopathic arthritis, each clinical trial design exhibits intrinsic limitations.[38] A notable limitation in this study is that, despite the geographical distribution of sites, there was a high prevalence of White participants, although this demographic is consistent with all published phase 3 trials in juvenile idiopathic arthritis.[7,10,11,15,32,37] A further potential limitation of this study, intrinsic to the randomised withdrawal study design, is that the clinical criterion and timing for randomised withdrawal was predetermined, meaning patient disease characteristics (eg, duration or depth of response) were not considered. Thus, the results might not be easily translated to real-world scenarios where these considerations could influence treatment disruption or discontinuation. Furthermore, baseline disease characteristics were evenly distributed among the patient population at randomisation. Although a subgroup analysis indicated directionally consistent results with the main outcome, the potential influence of other factors (eg, duration of disease and severity at baseline) on difference in response is indeterminable in this study.

Baricitinib is currently being evaluated in two phase 3 trials, in patients with systemic juvenile idiopathic arthritis (EudraCT 2017-004495-60; NCT04088396), and in patients with juvenile idiopathic arthritis-associated uveitis (EudraCT 2019-000119-10; NCT04088409). Patients enrolled in these baricitinib trials are able to transition to open-label long-term extensions. These long-term extensions will provide insights into the sustainable control of disease symptoms and potential context in the juvenile population for the rare events seen with baricitinib treatment in the adult population. Uveitis is a key extra-articular manifestation of juvenile idiopathic arthritis, and thus the study of baricitinib treatment for juvenile idiopathic arthritis-associated uveitis (or chronic anterior antinuclear antibody-positive uveitis) will provide insight on whether baricitinib is suitable in patients who do not respond or do not achieve long-lasting remission to current treatments, which is an unmet need.

In conclusion, this placebo-controlled trial showed the efficacy of baricitinib in the treatment of juvenile idiopathic arthritis. Baricitinib exposures in patients aged 2–8 years receiving 2 mg once a day and those aged 9–17 years receiving 4 mg once a day are similar to exposures in adult patients with rheumatoid arthritis receiving 4 mg once a day. Improvements in multiple disease activity and HQoL measures were observed in patients treated with baricitinib, which exceeded those of patients who were exposed to placebo during the study. Furthermore, the safety profile in this juvenile population was similar to that reported for adults. Taken together, our findings indicate a favourable risk–benefit balance of baricitinib in patients with juvenile idiopathic arthritis. Inhibition of JAK signalling by baricitinib can target multiple juvenile idiopathic arthritis-associated cytokine pathways and provides a once-daily oral therapeutic alternative to available therapies.

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Contributors

AVR, PQ, NO, IF, AS, ŠF, JA, HIB, and NR aided in the study conception and design. All study investigators aided in the acquisition of data. All authors had access to the data, and AVR, SK, and RL accessed and verified the underlying data. All authors were involved in the analysis and interpretation of data, and contributed to the drafting of this Article or revised it critically for important intellectual content. All authors approved the final version that was submitted for publication.

Declaration of interests

AVR has received consultancy fees from Eli Lilly and Company, AbbVie, Roche, GlaxoSmithKline, UCB, Novartis, Pfizer, and Sobi, and grant or research support from Eli Lilly and Company. PQ has received consultancy fees from Eli Lilly and Company. NO has received consultancy fees or payment for participation in speaker bureaus from Swedish Orphan Biovitrum, Eli Lilly and Company, AbbVie, Sanofi, Asahi Kasei Medical, Mitsubishi Tanabe Pharma, Bristol Myers Squibb, Pfizer Japan, Ayumi Pharma, Eisai, Torii Pharma, GlaxoSmithKline, Kyorin Pharma, Novartis, Chugai Pharmaceutical, Teijin Pharma, Amgen, and Astellas Pharma. IF has received consultancy fees from Eli Lilly and Company, Pfizer, Novartis, and Medac, travel support from Pfizer and Chugai, and grant or research support from Joachim Herz Stiftung. AS has received consultancy fees from Roche. ŠF has received payment or honoraria for a presentation from Novartis, and travel support from Sobi and AbbVie. JA has received consultancy fees or payment for participation in speaker bureaus from Eli Lilly and Company, GlaxoSmithKline, Amgen, Pfizer, and Novartis, grants or contracts from AbbVie, Sanofi, Amgen, Pfizer, and Novartis, and travel support from AbbVie and Pfizer. GM, JA, RL, and SK are employees of Eli Lilly and Company. ZW is an employee of Gilead Sciences, and former employee of Eli Lilly and Company; ZW provided statistical support for the analyses in this manuscript while employed with Elli Lily and Company. HIB has received payment for participation in speaker bureaus from GlaxoSmithKline, Novartis, Pfizer, and Roche; consultancy fees from Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Merck, Novartis, Eli Lilly and Company, Pfizer, Roche, and UCB; instructor fees from Novartis and Pfizer; and grant or research support from Bristol Myers Squibb and Pfizer. The funding from instructor fees, consulting, and grant or research support has been reinvested for research activities at HIB's employer, Cincinnati Children's Hospital, in a fully independent manner, without any commitment to third parties. NR has received consultancy fees or payment for participation in speaker bureaus from Eli Lilly and Company, Ablynx, Amgen, AstraZeneca, Aurinia, Bayer, Bristol Myers Squibb, Cambridge Healthcare Research, Celgene, Domain Therapeutics, Eli Lilly and Company, EMD Serono, GlaxoSmithKline, inMed Pharmaceuticals, Idorsia, Janssen, Novartis, Pfizer, Sobi, and UCB. NR is the senior scientist (unpaid) of the Paediatric Rheumatology International Trials Organisation (PRINTO). The IRCCS Istituto Giannina Gaslini, where NR works as a full-time public employee, has received contributions from Bristol Myers Squibb, Eli Lilly and Company, F Hoffman-La Roche, Novartis, Pfizer, and Sobi in the past 3 years. This funding has been reinvested for the research activities of the hospital in a fully independent manner, without any commitment to third parties.

Data sharing

Eli Lilly and Company will provide access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic and genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU or 6 months after acceptance of this Article for publication, whichever is later. No expiration date of data requests is currently set once data are made available. Access will be provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank and annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see https://vivli.org.

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