Tofacitinib as monotherapy following methotrexate withdrawal in patients with psoriatic arthritis previously treated with open-label tofacitinib plus methotrexate: a randomised, placebo-controlled sub-study of OPAL Balance

Peter Nash FRACP, Philip J Mease MD, Dona Fleishaker BSN, Joseph Wu PhD, Laura C Coates PhD, Frank Behrens MD, Dafna D Gladman MD, Alan J Kivitz MD, James C Wei MD, Ivan Shirinsky MD, Sujatha Menon PhD, Ana B Romero MD,* Lara Fallon PhD, Ming-Ann Hsu MPH, Cunshan Wang PhD, Keith S Kanik MD

Griffith University, Brisbane, Queensland, Australia (Peter Nash FRACP); **Swedish Medical Center/Providence St. Joseph Health and University of Washington, Seattle, WA, USA** (Philip J Mease MD); **Pfizer Inc, Groton, CT, USA** (Dona Fleishaker BSN, Joseph Wu PhD, Sujatha Menon PhD, Ming-Ann Hsu MPH, Cunshan Wang PhD, Keith S Kanik MD); **University of Oxford, Oxford, UK** (Laura C Coates PhD); **CIRI/Rheumatology University Hospital and Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Branch for Translational Medicine and Pharmacology TMP and Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD, Goethe University, Frankfurt, Germany** (Frank Behrens MD); **University of Toronto, Toronto Western Hospital, Krembil Research Institute, Toronto, ON, Canada** (Dafna D Gladman MD); **Altoona Center for Clinical Research, Duncansville, PA, USA** (Alan J Kivitz MD); **Department of Rheumatology & Immunology, Chung Shan Medical University Hospital and Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan** (James C Wei MD);

Federal State Budgetary Scientific Institution, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russia (Ivan Shirinsky MD); **Pfizer Inc, Barcelona, Spain** (Ana B Romero MD); **Pfizer Inc, Kirkland, QC, Canada** (Lara Fallon PhD)

**Former employee of Pfizer Inc*

Correspondence to:

Dona Fleishaker, c/o Sujatha Menon, Pfizer Inc, 558 Eastern Point Rd, Groton, CT 06340, USA. Email: dona.l.fleishaker@pfizer.com. Telephone number: +1 (248) 255 1542

Abstract word count: 298

Manuscript word count: 5,169

Number of figures/tables: 2 figures, 3 tables

Number of references: 26

Research in context

Evidence before this study

We conducted two PubMed searches (with no date restrictions) of English language publications reporting clinical trials of tofacitinib monotherapy or methotrexate withdrawal in patients with psoriatic arthritis (PsA). The first search utilised the terms ((‘tofacitinib’ [All Fields] OR ‘tofacitinib’ [MeSH Terms]) AND (‘monotherapy’ [All Fields]) AND (‘psoriatic arthritis’ [All Fields] OR ‘arthritis, psoriatic’ [MeSH Terms]) AND (Clinical Trial [Publication Type])). The second search utilised the terms ((‘tofacitinib’ [All Fields] OR ‘tofacitinib’ [MeSH Terms]) AND (‘methotrexate’ [All Fields] OR ‘methotrexate’ [MeSH Terms]) AND (‘withdrawal’ [All Fields] OR ‘withdrawn’ [All Fields] OR ‘discontinu*’ [All Fields] OR ‘monotherapy’ [All Fields]) AND (‘psoriatic arthritis’ [All Fields] OR ‘arthritis, psoriatic’ [MeSH Terms]) AND (Clinical Trial [Publication Type])). No relevant publications were retrieved.

Added value of this study

To our knowledge, this phase 3, randomised, double-blind, placebo-controlled, methotrexate withdrawal sub-study of the OPAL Balance long-term extension study (NCT01976364) was the first randomised clinical trial evaluating the efficacy and safety of tofacitinib monotherapy following withdrawal of background methotrexate (at doses of 7·5–20 mg/week) for the treatment of PsA. Results of this sub-study indicated that, on average, there were no appreciable differences in disease activity and physical function (per the co-primary endpoints of psoriatic arthritis disease activity score [PASDAS] and health assessment questionnaire-disability index, respectively, at month 6) between tofacitinib as monotherapy

following background methotrexate withdrawal versus tofacitinib with continued methotrexate. A numerical difference favouring continued background methotrexate was observed for PASDAS at month 9, but outcomes were similar in both treatment arms at month 12. The safety profile of tofacitinib was comparable between tofacitinib monotherapy and tofacitinib plus methotrexate, with the exception of a greater proportion of patients experiencing elevations in liver enzymes with continued methotrexate use compared with tofacitinib monotherapy.

Implications of all the available evidence

Methotrexate is a commonly used first-line treatment for PsA. In patients with an inadequate response to methotrexate, some clinical guidelines currently recommend treating patients with biologic disease-modifying antirheumatic drugs (bDMARDs) as monotherapy over in combination with methotrexate, whereas the 2019 EULAR guidelines recommend continuing methotrexate with a bDMARD in patients who tolerate methotrexate well, and reducing the methotrexate dose in patients showing a good response to the bDMARD. It may be possible to consider withdrawing background methotrexate, particularly in patients with a previous inadequate response to methotrexate. Previously, data for tofacitinib as monotherapy in PsA were lacking. The results of this study provide clinical evidence for the efficacy of tofacitinib as monotherapy following withdrawal of background methotrexate, in that some patients who have received ≥24 months' treatment with tofacitinib and who were receiving background methotrexate (at doses of 7·5–20 mg/week), may be able to discontinue methotrexate without a detrimental impact on their disease activity status or health-related quality of life over the next 12 months. As such, these findings are of particular relevance to clinical practice.

Summary

Background Tofacitinib is an oral Janus kinase inhibitor for the treatment of psoriatic arthritis (PsA), rheumatoid arthritis and ulcerative colitis. This study evaluated the efficacy and safety of tofacitinib 5 mg twice daily (BID) monotherapy after methotrexate withdrawal.

Methods OPAL Balance was an open-label, long-term extension study of tofacitinib in patients with PsA who participated in the OPAL Broaden and OPAL Beyond phase 3 studies. This 12-month, randomised, double-blind, placebo-controlled, methotrexate withdrawal sub-study (50 centres, 14 countries) included patients from OPAL Balance who completed ≥24 months' tofacitinib treatment (≥3 months' stable tofacitinib 5 mg BID) and were receiving methotrexate (7·5–20 mg/week). Patients, randomised 1:1 using interactive response technology, received open-label tofacitinib 5 mg BID with blinded placebo (tofacitinib monotherapy) or blinded, continued methotrexate (tofacitinib+methotrexate). Co-primary endpoints were changes from sub-study baseline (Δ) in psoriatic arthritis disease activity score (PASDAS) and health assessment questionnaire-disability index (HAQ-DI) at month 6 in all randomised patients with ≥1 sub-study drug dose. Safety was assessed throughout. No specific statistical hypothesis was tested. The study (OPAL Balance) is registered with ClinicalTrials.gov (NCT01976364) and is complete.

Findings Between 30/10/2017 and 20/05/2019, 180 patients were randomised and 179 were treated (tofacitinib monotherapy, n=90; tofacitinib+methotrexate, n=89). At month 6, least squares mean (LSM) (standard error) ΔPASDAS were 0·23 (0·08) for tofacitinib monotherapy and 0·14 (0·08) for tofacitinib+methotrexate (treatment difference: LSM 0·09 [95% confidence interval (CI) -0·13, 0·31]), and ΔHAQ-DI were 0·04 (0·03) and 0·02

(0·03), respectively (treatment difference: 0·03 [-0·05, 0·10]). Rates of adverse events (AEs), discontinuations due to AEs, AEs of special interest, and laboratory changes were generally comparable between treatment arms, although liver enzyme elevations were more common with tofacitinib+methotrexate.

Interpretation Some patients with PsA stable on tofacitinib 5 mg BID with background methotrexate may be able to discontinue methotrexate without clinically meaningful changes in disease activity and safety.

Funding: Pfizer Inc.

Keywords: Methotrexate; Psoriatic Arthritis; Tofacitinib

Introduction

Psoriatic arthritis (PsA) is a chronic, immune-mediated disease that manifests as peripheral joint inflammation and destruction, skin and nail psoriasis, enthesitis, dactylitis, and spondylitis.[1,2]

Methotrexate is frequently used as a first-line PsA treatment,[3] and recommendations suggest that the optimal initial dose reaches 25 mg/week.[4] Non-placebo-controlled clinical studies of methotrexate monotherapy at doses ≥15 mg/week (TICOPA, SEAM-PsA, and RESPOND studies) have demonstrated improvements in clinical outcomes such as joint counts, skin, enthesitis, dactylitis, and patient-reported outcomes (PROs).[5–7] In our experience, many patients fail to respond to methotrexate, and experience known tolerability issues, such as hepatotoxicity and gastrointestinal adverse events (AEs).[8,9] In patients with an inadequate response to methotrexate, some clinical guidelines have favoured replacing methotrexate with an advanced therapy rather than adding to it.[8] However, the 2019 EULAR guidelines recommend continuing methotrexate with advanced therapies in patients who tolerate methotrexate well, and reducing the methotrexate dose in patients showing a good response to biological treatment, especially if there are concerns about toxicity.[4]

Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA, rheumatoid arthritis, and ulcerative colitis. For PsA, tofacitinib is approved for use in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).[10] The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) have been demonstrated in two phase 3 randomised controlled trials (RCTs) in patients with active PsA.[11,12] Tumour necrosis factor inhibitor (TNFi)-naïve patients with an inadequate response to ≥1 csDMARD were included in the 12-

month OPAL Broaden study,[11] and patients with an inadequate response to ≥1 TNFi were included in the 6-month OPAL Beyond study.[12] In both studies, patients were required to remain on a stable dose of one background csDMARD (mostly methotrexate [79% across both studies]). Eligible patients from both studies could continue to receive tofacitinib (with or without background csDMARD therapy) in a long-term extension (LTE) study, OPAL Balance.[13] On day 1 of OPAL Balance, 80% of patients were receiving methotrexate.[13]

To date, tofacitinib has not previously been assessed as monotherapy in an RCT for the treatment of PsA. Here, we present a sub-study of the OPAL Balance LTE study that examined the efficacy, safety, and tolerability of tofacitinib 5 mg BID as monotherapy after methotrexate withdrawal, versus tofacitinib 5 mg BID with continued background methotrexate, in patients with PsA. The results of this analysis may be used to assess whether background methotrexate may be withdrawn in patients with PsA who are receiving tofacitinib.

Methods

Study design

The OPAL Balance LTE study (NCT01976364; N=686) was an open-label, 36-month study, conducted in 124 centres across 16 countries (Australia, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Germany, Hungary, Mexico, Poland, Russia, Slovakia, Spain, Taiwan, UK, and US) (completed 23 January 2019; database released 29 July 2019). Adult patients with active PsA had participated in prior qualifying phase 3 studies OPAL Broaden (NCT01877668) or OPAL Beyond (NCT01882439) (full eligibility criteria reported previously).[11,12] In the LTE study, all patients received open-label tofacitinib 5 mg BID, with

concomitant csDMARDs permitted, regardless of qualifying study treatment (see appendix figure S1).

The methotrexate withdrawal sub-study of the OPAL Balance LTE study was a phase 3, randomised, double-blind, placebo-controlled, parallel-group, 12-month estimation study (appendix figure S1). Patients were from 50 centres across 14 countries (Australia, Belgium, Bulgaria, Czech Republic, Germany, Hungary, Mexico, Poland, Russia, Slovakia, Spain, Taiwan, UK, and US) (completed 20 May 2019; database released 31 July 2019).

OPAL Balance was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and applicable local regulatory requirements and laws. The study protocol was approved by the Institutional Review Boards and/or Independent Ethics Committee at each study centre.

Patients

Patients were eligible to enter the OPAL Balance LTE study ≤3 months after completing the qualifying study, or discontinuing for reasons other than study-drug related AEs. Full eligibility criteria for the LTE study are included in the appendix.

Patients were eligible to enter the OPAL Balance sub-study if they received the following during the LTE study: tofacitinib treatment for ≥24 months, stable at 5 mg BID for ≥3 months; and a stable dose of oral methotrexate (7·5–20 mg/week) for ≥4 weeks. They must also have completed all sub-study switch/baseline visit procedures as required. There was no requirement for PsA disease activity to enter the sub-study.

Patients were excluded from the sub-study if they were receiving other concomitant csDMARDs, were receiving methotrexate by a route other than oral administration, or were receiving methotrexate at a dose <7·5 mg/week or >20 mg/week. Additional inclusion and exclusion criteria are included in the appendix. All patients provided written, informed consent.

Randomisation and masking

The OPAL Balance sub-study switch/baseline visit (hereafter referred to as baseline) occurred at a scheduled study visit on or after month 24 of the LTE study (appendix figure S1). Eligible patients were randomised (1:1) using interactive response technology to receive open-label tofacitinib 5 mg BID plus placebo (i.e., underwent methotrexate withdrawal to receive tofacitinib as monotherapy and matched methotrexate placebo) or open-label tofacitinib 5 mg BID plus methotrexate (i.e., continuation of background methotrexate). Methotrexate and the matched placebo were blinded to patients, investigators, and the sponsor. At the baseline visit, blinded study co-ordinators entered select patient information to generate a randomisation code and container number(s) for the supply of the investigational product.

Procedures

In the OPAL Balance sub-study, tofacitinib, blinded methotrexate, and the corresponding methotrexate placebo were self-administered by patients. The methotrexate dose must have been identical to that taken before sub-study entry with dose reductions permitted on evidence of toxicity. Methotrexate withdrawal was immediate and not tapered, and the tofacitinib dose must have remained stable at 5 mg BID throughout the sub-study. Sub-study

treatment continued until the patient discontinued or received 12 months of treatment.

Physical examinations were conducted, and efficacy outcomes and PROs were assessed at sub-study baseline and at months 1, 3, 6, 9, and 12. Laboratory tests and AE reporting were assessed throughout the sub-study.

Outcomes

The primary objective of the OPAL Balance sub-study was to assess the efficacy of tofacitinib 5 mg BID plus placebo versus tofacitinib 5 mg BID plus methotrexate. Safety and tolerability of the two treatment regimens was a secondary objective. The co-primary efficacy endpoints were change from baseline at month 6 in psoriatic arthritis disease activity score (PASDAS; higher scores indicate higher disease activity) and health assessment questionnaire-disability index (HAQ-DI; range 0–3; higher scores indicate greater disability).

Secondary efficacy outcomes included musculoskeletal and dermatological outcomes, composite outcomes and PROs. Musculoskeletal and dermatologic outcomes included change from baseline in: PASDAS (other than at month 6); HAQ-DI (other than at month 6); and Leeds enthesitis index (LEI; range 0–6; higher scores indicate more affected sites) in patients with baseline LEI >0. Additionally, LEI in patients with baseline LEI=0, the proportion of patients maintaining absence of enthesitis (LEI=0) in patients with baseline LEI=0, dactylitis severity score (DSS; range 0–60; higher scores indicate greater severity) in patients with baseline DSS=0, and the proportion of patients maintaining absence of dactylitis (DSS=0) in patients with baseline DSS=0 were assessed. Change from baseline in DSS was not reported due to insufficient patient numbers with baseline DSS >0.

Changes from baseline in the following secondary outcomes were also assessed:

tender/painful joint counts out of 68 joints (TJC [68]; higher scores indicate a greater number of tender/painful joints); swollen joint counts out of 66 joints (SJC [66]; higher scores indicate a greater number of inflamed joints); physician global assessment of arthritis (PGA) visual analogue scale (VAS; range 0–100 [mm]; higher scores indicate worse disease activity); C-reactive protein (CRP); and physician global assessment of psoriasis (PGA-PsO; range 0–4 [clear–severe]) in patients with baseline PGA-PsO >0. Percent change from baseline in body surface area (BSA; range 0–100%; higher percentages indicate a larger affected area) affected by plaque psoriasis was also evaluated in patients with baseline BSA >0%.

One composite outcome was the proportion of patients achieving minimal disease activity (MDA), defined as achieving ≥5 of the following seven criteria: TJC [68] ≤1; SJC [66] ≤1; BSA ≤3%; patient global assessment of arthritis (PtGA) VAS ≤20 mm; patient's assessment of arthritis pain VAS (Pain; range 0–100 [mm]; higher score indicates greater pain) ≤15 mm; HAQ-DI score ≤0·5; and tender entheseal points (using LEI) ≤1.[14] Another was the proportion of patients achieving PsA response criteria (PsARC), defined as improvement in two of the following four criteria, one of which must be joint pain or swelling, without worsening in any measure: ≥30% improvement in TJC [68] or SJC [66], and ≥20% improvement in PtGA or PGA.[15,16]

Although Psoriasis Area and Severity Index (PASI) and Disease Activity in Psoriatic Arthritis were assessed in the OPAL Balance LTE study, these outcome measures were not included in the sub-study, in order to decrease the burden on patients and reduce the number of assessments completed. Moreover, PASI requires patients to have ≥3% BSA affected by psoriasis, and it was expected that most patients in this sub-study would not meet this

requirement.

Changes from baseline in the following PROs were evaluated: PtGA VAS (range 0–100 [mm]; higher score indicates worse disease activity); pain VAS; patient's global joint and skin assessment (PGJS) VAS (range 0–100 [mm]; global question; higher score indicates greater joint and skin involvement) (this was considered to be an "other" endpoint); short form-36 health survey (version 2, acute; SF-36v2) physical component summary (PCS) and mental component summary (MCS) scores, and eight norm-based domain scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health; lower scores indicate a worse health outcome); functional assessment of chronic illness therapy-fatigue (FACIT-F) total score (range 0–52; lower scores indicate more fatigue); EuroQoL-five dimensions-three level health questionnaire (EQ-5D-3L; dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression; range 1–3; higher scores indicate greater impact on dimension); and an EQ-VAS score (range 0–100 [mm]; lower scores indicate a worse health state) on 'Your own health state today'.

Post-hoc analyses were conducted to assess if baseline disease activity impacted tofacitinib efficacy following methotrexate withdrawal. Primary and secondary endpoints were assessed in patients with or without baseline low disease activity (LDA) (per baseline PASDAS ≤3·2 vs >3·2, respectively), and in patients with or without baseline MDA. Additional post-hoc analyses assessed whether there was a shift in the proportion of patients with response (per PASDAS ≤3·2, MDA or PGA-PsO score of 0 or 1) or BSA clearance (BSA 0%) from baseline to months 6 and 12.

Safety outcomes included all AEs, serious AEs (SAEs), discontinuations due to AEs, AEs of special interest (AESI; herpes zoster, serious infections, opportunistic infections, gastrointestinal perforations, malignancies excluding non-melanoma skin cancer [NMSC], NMSC, major adverse cardiovascular events [MACE], interstitial lung disease [ILD], venous thromboembolisms [including deep vein thrombosis (DVT) and pulmonary embolism (PE)], and arterial thromboembolisms), deaths, clinical laboratory abnormalities, and changes from baseline in laboratory values.

Statistical analysis

A sample size of 90 patients per treatment arm was selected for the sub-study to allow a two-sided 95% confidence interval (CI) half-width for a between-group difference in HAQ-DI change from baseline at month 6 of approximately 0·18 assuming a common standard deviation of 0·6 for both arms. This sample size would yield a two-sided 95% CI half-width of approximately 0·47 for the difference in PASDAS change from baseline at month 6 between the treatment arms assuming a common standard deviation of 1·6 for both arms. This was an estimation study, primarily driven by the anticipated small sample size; therefore, no specific statistical hypothesis (either superiority or non-inferiority) was tested and no adjustment for multiple comparisons was made.

Efficacy was assessed in the full analysis set (FAS), which included all patients who were randomised in the sub-study and received ≥1 dose of sub-study drug (tofacitinib, methotrexate, or placebo). A per protocol analysis was not defined. Safety was assessed in the safety analysis set, which was identical to the FAS.

Continuous efficacy and PRO endpoints required that a patient had a baseline value and ≥1

post-baseline values for inclusion in the FAS for that endpoint. Changes from baseline in continuous endpoints were analysed using a mixed model for repeated measures with fixed effects of treatment, visit, treatment-by-visit interaction, and baseline value without imputation for missing values including data up to month 12; a common unstructured covariance matrix was used. Binary efficacy endpoints were analysed using the normal approximation for the difference in binomial proportions with missing response as non-response. Interval estimation using 95% CI for the between-group treatment difference was reported; differences were noted when the 95% CI excluded 0. Safety data were summarised descriptively. All statistical analyses were performed using SAS Version 9·4.

An external data monitoring committee was responsible for ongoing monitoring of the efficacy and safety of patients in the sub-study. External adjudication committees were established to standardise the assessment of selected safety events, including cardiovascular events, opportunistic infections, malignancies, hepatic events, and gastrointestinal perforations. An internal adjudication committee was established to review and categorise events of ILD.

This study (OPAL Balance) is registered with ClinicalTrials.gov (NCT01976364) and is complete.

Role of the funding source

The study sponsor was involved in study design and data collection. All authors were involved in data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 30 October 2017 and 20 May 2019, 180 patients from the OPAL Balance LTE study entered the sub-study and 179 were treated in the sub-study. Overall, 90 patients received tofacitinib 5 mg BID plus placebo, and 89 patients received tofacitinib 5 mg BID plus methotrexate (figure 1). A similar proportion of patients completed or discontinued treatment in each treatment arm. The mean (range) duration of study drug treatment during the sub-study was 327·7 (54–358) days for tofacitinib 5 mg BID plus placebo and 319·1 (28–364) days for tofacitinib 5 mg BID plus methotrexate. Demographics and baseline disease characteristics were generally similar between treatment arms (table 1). The proportion of patients with PASDAS-LDA (≤3·2) at baseline was higher in the tofacitinib 5 mg BID plus placebo arm than the tofacitinib 5 mg BID plus methotrexate arm, which corresponded with the proportion of patients with baseline MDA. Baseline PASDAS and HAQ-DI scores were similar between treatment arms. The mean methotrexate dose at baseline was 15·3 mg/week in the tofacitinib 5 mg BID plus placebo arm, and 14·6 mg/week in the tofacitinib 5 mg BID plus methotrexate arm.

At month 6, no differences were observed in change from baseline in PASDAS and HAQ-DI (co-primary endpoints) between patients receiving tofacitinib 5 mg BID plus placebo and tofacitinib 5 mg BID plus methotrexate (figure 2). Least squares mean (LSM) (standard error; SE) changes in PASDAS were 0·23 (0·08) for tofacitinib 5 mg BID plus placebo and 0·14 (0·08) for tofacitinib 5 mg BID plus methotrexate at month 6, with a treatment difference (95% CI) of 0·09 (-0·13, 0·31). LSM (SE) changes in HAQ-DI were 0·04 (0·03) for tofacitinib 5 mg BID plus placebo and 0·02 (0·03) for tofacitinib 5 mg BID plus methotrexate, with a treatment difference (95% CI) of 0·03 (-0·05, 0·10). For changes from

baseline in PASDAS and HAQ-DI at each time point, the 95% CI of the LSM difference between arms included 0 (appendix table S1). At month 9, LSM (SE) changes from baseline in PASDAS were numerically higher for tofacitinib 5 mg BID plus placebo versus tofacitinib 5 mg BID plus methotrexate (0·37 [0·09] vs 0·16 [0·09]), but outcomes were similar at month 12 (0·13 [0·09] vs 0·19 [0·09]) (appendix table S1).

In general, secondary clinical efficacy outcomes were similar between treatment arms at months 6 and 12 (table 2). Change from baseline in PGA-PsO at month 6 was greater (indicating worsening of psoriasis), and the proportions of patients achieving PsARC response at month 12 were lower with tofacitinib 5 mg BID plus placebo versus tofacitinib 5 mg BID plus methotrexate. MDA rates were generally maintained to month 12 regardless of methotrexate withdrawal (appendix figure S2[A]), with observed changes primarily due to decreases in the TJC and BSA components in the tofacitinib 5 mg BID plus placebo arm, and the LEI component in the tofacitinib 5 mg BID plus methotrexate arm.

The proportions of patients with absence of enthesitis or dactylitis were maintained for patients with LEI=0 or DSS=0 at baseline, respectively (appendix figure S2[B&C]).

Change from baseline in PROs (PtGA VAS, pain VAS, PGJS VAS, SF-36v2 PCS and MCS scores, FACIT-F total score, and SF-36v2 domain scores) were similar between treatment arms over time (table 2, appendix figure S3, and appendix table S2).

There was a numerical difference favouring tofacitinib 5 mg BID plus methotrexate observed in the EQ-VAS scale (‘Your own health state today’) at month 6, with 95% CI of the treatment difference excluding 0 (table 2). No differences were observed at any other time points, or in the other five EQ-5D-3L dimension scores (appendix table S3).

In post-hoc analyses in patients stratified by achievement of PASDAS-defined LDA and MDA at baseline, LSM changes from baseline in PASDAS and HAQ-DI at months 6 and 12 were generally similar between tofacitinib 5 mg BID plus placebo and tofacitinib 5 mg BID plus methotrexate, regardless of baseline disease activity (appendix figure S4). A trend towards an increase in PASDAS was apparent, showing worsening disease activity, in patients without versus those with baseline MDA, at months 6 and 12 in both treatment arms. Secondary clinical efficacy outcomes and PROs also showed generally similar results between treatment arms, regardless of baseline disease activity (data not shown). In post-hoc analyses of the shift in responders from baseline to months 6 and 12, the majority of patients who were responders at baseline maintained their response at months 6 (PASDAS, 81% and 80%; MDA, 74% and 80%; PGA-PsO, 79% and 86%, for tofacitinib 5 mg BID plus placebo and tofacitinib 5 mg BID plus methotrexate, respectively) and 12 (PASDAS, 78% and 71%; MDA, 68% and 78%; PGA-PsO, 71% and 83%, for tofacitinib 5 mg BID plus placebo and tofacitinib 5 mg BID plus methotrexate, respectively). In addition, the majority of patients who had BSA clearance at baseline maintained this at months 6 and 12 (85% and 79%, respectively, for tofacitinib 5 mg BID plus placebo, and 90% and 86%, respectively, for tofacitinib 5 mg plus methotrexate). Response/BSA clearance shift patterns at months 6 and 12 were generally similar between treatment groups (appendix figure S5).

The incidence of all-cause AEs was similar between the tofacitinib 5 mg BID plus placebo and tofacitinib 5 mg BID plus methotrexate arms to month 12 (table 3). Most AEs were mild or moderate in severity. The incidences of SAEs and discontinuations due to AEs were also similar between the two treatment arms. No deaths occurred in the sub-study. Overall, the most common AEs reported in the two treatment arms were upper respiratory tract infection

and urinary tract infection. Flares of worsening symptoms was reported in one (1%) patient in the tofacitinib 5 mg BID plus placebo arm (recorded as psoriatic arthropathy). This patient had received baseline methotrexate at a dose of 15 mg/week, prior to methotrexate withdrawal. The patient had been withdrawn from the study 12 days prior to the onset of psoriatic arthropathy due to a protocol violation, as tofacitinib had been withheld for 54 days (which exceeded the 14 consecutive days allowed per protocol) due to a non-serious event of herpes zoster. Three (3%) patients receiving tofacitinib 5 mg BID plus methotrexate reported flares of worsening symptoms (recorded as psoriatic arthropathy for all patients; two [2%] patients discontinued). These patients were receiving methotrexate at the same doses of 15 or 20 mg/week at baseline and during the sub-study (one patient had received methotrexate 25 mg/week in the LTE study but decreased to 20 mg/week upon entry to the sub-study, per protocol).

AESI were infrequent and occurred in similar proportions of patients in each treatment arm (table 3). In total, two (2%) patients receiving tofacitinib 5 mg BID plus methotrexate experienced serious infections; of these, one reported appendicitis and the other reported both multidermatomal herpes zoster and pneumonia herpes viral. In the latter patient, blood cultures were negative for anaerobic and aerobic bacteria, and there were no sputum cultures obtained to confirm the pneumonia diagnosis. Both the multidermatomal herpes zoster and pneumonia herpes viral events were adjudicated as opportunistic infections; no other events were adjudicated as opportunistic infections.

One (1%) malignancy (adjudicated) was reported in each treatment arm; these were bladder cancer (tofacitinib 5 mg BID plus placebo) and Bowen's disease (tofacitinib 5 mg BID plus methotrexate). One (1%) arterial thromboembolism was reported in the tofacitinib 5 mg BID

plus placebo arm; this patient experienced a non-serious, carotid artery occlusion that was adjudicated as not a cardiovascular event. No events of NMSC, MACE, DVT, PE, gastrointestinal perforations, or ILD were reported in either treatment arm.

A numerically lower proportion of patients experienced elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) from baseline in the tofacitinib 5 mg BID plus placebo versus tofacitinib 5 mg BID plus methotrexate arm (table 3).

Absolute neutrophil counts (ANC) and absolute lymphocyte counts (ALC) increased with tofacitinib 5 mg BID plus placebo, and decreased with tofacitinib 5 mg BID plus methotrexate, from baseline to months 6 and 12 (table 3). ALT and AST decreased with tofacitinib 5 mg BID plus placebo and increased with tofacitinib 5 mg BID plus methotrexate, from baseline to months 6 and 12 (table 3).

The proportions of patients with laboratory test abnormalities, including abnormalities in liver parameters, were similar in both treatment arms. The only differences noted were in increases in creatine kinase, which were more frequent in the tofacitinib 5 mg BID plus placebo arm, and decreases in ALC, which were more frequent in the tofacitinib 5 mg BID plus methotrexate arm (appendix table S4). In the tofacitinib 5 mg BID plus placebo arm, monitoring criteria were met for haemoglobin (decrease >2g/dL below baseline) in three (3%) patients, serum creatinine increase (>50% or >0·5 mg/dL over baseline value) in one (1%) patient, and creatine kinase (>5×upper limit of normal [ULN]) in six (7%) patients. In the tofacitinib 5 mg BID plus methotrexate arm, monitoring criteria were met for haemoglobin (decrease >2g/dL below baseline) in eight (9%) patients, ANC (<$1{\cdot}2\times10^3$/mm^3)

in one (1%) patient, ALC (<0·5×10^3/mm^3) in two (2%) patients, and creatine kinase (>5×ULN) in one (1%) patient. No patients in either arm met discontinuation criteria (i.e., values were not confirmed by two sequential measurements) for any laboratory parameter.

Discussion

The OPAL Balance sub-study in patients with PsA who had received open-label tofacitinib for at least 24 months, evaluated the efficacy, safety, and tolerability of tofacitinib 5 mg BID as monotherapy (after methotrexate withdrawal), versus with continued background methotrexate. To date, this is the first RCT to assess tofacitinib as monotherapy for the treatment of PsA. On average, no clinically meaningful differences in efficacy were observed with open-label tofacitinib 5 mg BID as monotherapy after blinded methotrexate withdrawal versus tofacitinib 5 mg BID with blinded continued methotrexate. The safety profile was similar in each treatment arm, except for a greater proportion of patients experiencing liver enzyme elevations with tofacitinib 5 mg BID plus methotrexate. Collectively, within the parameters of this study, these results suggest the feasibility of discontinuing methotrexate in patients who have received tofacitinib in combination with methotrexate.

The co-primary endpoints of the sub-study assessed disease activity and physical function (change from baseline in PASDAS and HAQ-DI at month 6, respectively). HAQ-DI was included as one of the primary endpoints in the qualifying studies, and for this sub-study, HAQ-DI was considered to be a measure sensitive to whether PsA worsened following the withdrawal of methotrexate.

Across all time points, mean changes from baseline in PASDAS and HAQ-DI, as well as treatment differences for both outcomes, were below the measurement error and minimum

clinically important difference for PASDAS (0·8) and HAQ-DI (0·35), respectively, indicating that, on average, both the changes from baseline and the differences between treatment arms were not clinically meaningful.[17,18] Secondary clinical efficacy outcomes assessing disease activity also remained stable throughout the sub-study for patients receiving tofacitinib, whether in combination with methotrexate or as monotherapy after methotrexate withdrawal. A difference was observed for PGA-PsO at month 6, indicating a worsening of psoriasis in some tofacitinib-treated patients who withdrew methotrexate. The authors have also observed this in clinical practice in some PsA patients receiving bDMARDs who discontinue methotrexate. PsARC response rates at month 12 were lower in patients receiving tofacitinib as monotherapy than with continued methotrexate. MDA rates were maintained at ≥40% throughout the 12-month period, and were generally similar for both treatment arms. Rates of enthesitis and dactylitis absence were also maintained at ≥80% up to month 12.

Similarly, methotrexate withdrawal did not substantially impact the PRO improvements reported with tofacitinib; an exception was worsened overall health (shown by a decrease in EQ-VAS) with tofacitinib as monotherapy versus with continued methotrexate at month 6, with no difference at any other time points.

At baseline, most patients (66%) had PASDAS-LDA (≤3·2), although a numerically higher proportion had PASDAS-LDA or MDA in the tofacitinib 5 mg BID plus placebo arm versus the tofacitinib 5 mg BID plus methotrexate arm. Results of the post-hoc analyses indicated that efficacy outcomes and PROs were generally consistent between the two treatment arms, regardless of baseline disease activity. The response/BSA clearance shift patterns were similar between treatment arms at months 6 and 12. The majority of patients who had responded to treatment at baseline remained responders at months 6 and 12, regardless of

methotrexate withdrawal, although a minority of patients in both treatment arms became non-responders. Similarly, there were some non-responders at baseline who became responders at months 6 and 12, across both treatment arms.

The incidence of all-cause AEs, SAEs, and discontinuations due to AEs was similar in each treatment arm. A similar proportion of patients in either treatment arm experienced flares as worsening in symptoms (recorded as psoriatic arthropathy), which led to discontinuation of two (2%) patients in the tofacitinib 5 mg BID plus methotrexate arm. There were no deaths and AESI were infrequently reported.

Hepatotoxicity is a known safety concern associated with methotrexate use in patients with PsA,[8,9] and an increased incidence of liver enzyme elevation has previously been observed with tofacitinib, primarily in studies with background DMARD therapy (most commonly methotrexate).[10] Laboratory changes were similar between treatment arms of this sub-study, except for a greater proportion of patients experiencing liver enzyme (ALT and AST) elevations with tofacitinib with continued methotrexate versus following methotrexate withdrawal. No patient met protocol-defined discontinuation criteria relating to liver parameters in this sub-study.

Overall, tofacitinib safety in this sub-study was consistent with previously reported findings from the OPAL Broaden[11] and OPAL Beyond[12] qualifying phase 3 studies, interim data from the OPAL Balance LTE study,[13] and an analysis of safety data pooled from the phase 3 and LTE tofacitinib PsA studies.[19]

Treat-to-target, including withdrawal/tapering of medication in patients who achieve treatment goals, is still an emerging concept in PsA.[8,20] The impact of background

methotrexate in combination with advanced therapies in the treatment of PsA is an area of interest. A recent retrospective analysis of clinical data with adalimumab demonstrated that withdrawal of methotrexate (mean dose 12·8 mg/week) had little impact on the efficacy of adalimumab in patients with PsA; however, in the same analysis, it was noted that the addition of methotrexate to adalimumab in patients with rheumatoid arthritis was associated with greater efficacy compared with adalimumab monotherapy.[21] Similarly, analyses of real-world data have shown that the efficacy of TNFi does not appear to be affected by concomitant methotrexate (mean dose 14·7 mg/week) in patients with PsA, although concomitant methotrexate may improve persistence with monoclonal antibodies, particularly infliximab.[22,23] The results of this sub-study are also consistent with those of a recent phase 3b/4 study of tofacitinib in patients with rheumatoid arthritis, in that background methotrexate (mean dose 16·4–16·9 mg/week) could be withdrawn in most patients with an inadequate response to methotrexate who achieved LDA with tofacitinib 11 mg once daily plus methotrexate, without significant worsening of disease activity or emergence of unanticipated safety issues;[24] numerically higher liver enzyme abnormalities were also observed with continued methotrexate. While patients in this sub-study were not required to achieve LDA before methotrexate withdrawal, those entering had presumably responded well to, and tolerated, long-term treatment with tofacitinib in the associated LTE study. It is therefore possible that patients with an inadequate response to methotrexate who are receiving advanced therapies in combination with methotrexate may be able to withdraw methotrexate without a significant impact on disease activity.

It is fair to comment that withdrawal of background methotrexate from tofacitinib treatment may not affect clinical response if the methotrexate dose was suboptimal. In this study, it was

not possible to determine whether patients on higher doses of methotrexate were more likely to experience flare on methotrexate withdrawal than those receiving lower doses, as the maximum dose of methotrexate that patients could receive was 20 mg/week, per protocol. The mean methotrexate dose at sub-study baseline was approximately 15 mg/week, which was similar to the above real-world[21,23] and clinical studies, and other real-world settings (where it was reported that patients with PsA received average methotrexate doses of approximately 15–20 mg/week).[25,26] Consistent with this, the patient in the tofacitinib 5 mg BID plus placebo arm who experienced flare had received baseline methotrexate 15 mg/week (i.e., prior to withdrawal); this patient had also discontinued tofacitinib prior to the onset of the flare.

Limitations of this analysis include that the study was not powered for hypothesis testing, by design. Additionally, this sub-study was conducted in patients from OPAL Balance, who had responded well to, and tolerated, tofacitinib and methotrexate long-term treatment. Taken together with the limited number of patients in this sub-study, differences in safety were expected to be minimal. Furthermore, methotrexate was immediately withdrawn and not tapered in any way, which may not reflect clinical practice. Moreover, in clinical practice, disease control is likely to be achieved before withdrawal or tapering of methotrexate, whereas patients entering this sub-study were not required to have achieved disease control (although the majority of patients had LDA at baseline). As such, the results may not be fully representative of patients in a real-world setting. The majority (>90%) of patients were white, which may also further limit the generalisability of the study. A further limitation is that improvements in some outcomes, such as DSS, could not be assessed due to the low number of patients with these symptoms at baseline. Future analyses should include assessments of

tofacitinib monotherapy in patients reporting flare or worsening of PsA.

In conclusion, the results of this sub-study provide further characterisation of the efficacy of tofacitinib in patients with PsA, and suggest that some patients receiving tofacitinib 5 mg BID with background methotrexate who are in a stable disease state may be able to discontinue methotrexate to receive tofacitinib monotherapy, without an adverse impact on their overall disease activity or health-related quality of life.

Contributors

KSK, DF, JW, SM, M-AH, and CW conceived, designed, and/or conducted the study. PN, PJM, JCW, FB, AJK, and IS acquired data. JW and CW analysed the data. All authors were involved in interpretation of data and reviewed and approved the manuscript's content before submission.

Declaration of interests

PN has received research grants and consulting fees from, and is a member of the speakers' bureau for, AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, MSD, Novartis, Pfizer Inc, Roche, Sanofi, and UCB.

PJM has received research grants from AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer Inc, Sun, and UCB; has received consulting fees from AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Novartis, Pfizer Inc, Sun, and UCB; and is a member of the speakers' bureau for AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly, Genentech, Janssen, Novartis, Pfizer Inc, and UCB.

LCC has received research grants from AbbVie, Celgene, Eli Lilly, Novartis, and Pfizer Inc; has received consulting fees from AbbVie, Amgen, Celgene, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, and Pfizer Inc; and has received honoraria from AbbVie, Amgen, Biogen, Eli Lilly, Novartis, Pfizer Inc, and UCB.

FB has received research grants from Celgene, Chugai, Janssen, Pfizer Inc, and Roche; and has received consulting fees from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chugai, Eli Lilly, Galapagos, Genzyme, Gilead, Janssen, MSD, Novartis, Pfizer Inc, Roche, Sandoz, Sanofi, and UCB.

DDG has received grant/research support from AbbVie, Amgen, Celgene, Eli Lilly, Novartis, Pfizer Inc, and UCB; and has received consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer Inc, and UCB.

AJK has stock ownership from AbbVie, Amgen, Gilead, GSK, Novartis, and Sanofi; has received consulting fees from Gilead, Pfizer Inc, Regeneron, Sanofi, and SUN Pharma Advanced Research; is a member of the Advisory Committee or Review Panel of AbbVie, Boehringer Ingelheim, Genzyme, Janssen, Pfizer Inc, Sanofi, Regeneron, and UCB; is a member of the Advisory Board for Genentech; is a member of the Speaker and Steering Committee for Flexion; and has received payment for speaking and teaching/training from Celgene, Genzyme, Horizon, Merck, Novartis, Pfizer Inc, Regeneron, and Sanofi. Altoona Research Center for Clinical Research, PC, at which AJK is employed, received financial support for participating in this clinical research trial.

JCW has received research grants from AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, and UCB; and has received consulting fees or other

remuneration from AbbVie, Bristol-Myers Squibb, Celgene, Chugai, Eisai, Janssen, Novartis, Pfizer Inc, Sanofi-Aventis, and UCB Pharma.

IS has no disclosures to declare.

DF, JW, SM, LF, M-AH, CW, and KSK are employees and shareholders of Pfizer Inc.

ABR was an employee and shareholder of Pfizer Inc at the time of this analysis.

Acknowledgments

This study was sponsored by Pfizer Inc. The authors wish to thank the patients and investigators involved in this study. Medical writing support, under the guidance of the authors, was provided by Christina Viegelmann, PhD, CMC Connect, McCann Health Medical Communications, and was funded by Pfizer Inc, New York, NY, USA in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015; **163**: 461–464).

Data availability

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU, or (2) in programmes that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may 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.

References

1 Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005; **64**: ii14–7.

2 Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med* 2017; **376**: 957–70.

3 Ceponis A, Kavanaugh A. Use of methotrexate in patients with psoriatic arthritis. *Clin Exp Rheumatol* 2010; **28**: S132–7.

4 Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020; **79**: 700–12.

5 Coates LC, Helliwell PS. Methotrexate efficacy in the Tight Control in Psoriatic Arthritis study. *J Rheumatol* 2016; **43**: 356–61.

6 Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled Phase III trial. *Arthritis Rheumatol* 2019; **71**: 1112–24.

7 Baranauskaite A, Raffayová H, Kungurov NV, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. *Ann Rheum Dis* 2012; **71**: 541–8.

8 Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis.

Arthritis Care Res (Hoboken) 2019; **71**: 2–29.

9 Tilling L, Townsend S, David J. Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis. *Clin Drug Investig* 2006; **26**: 55–62.

10 Pfizer Inc. XELJANZ prescribing information. 2019. https://labeling.pfizer.com/ShowLabeling.aspx?id=959 (accessed 11 February 2020).

11 Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med* 2017; **377**: 1537–50.

12 Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med* 2017; **377**: 1525–36.

13 Nash P, Coates LC, Kivitz AJ, et al. Safety and efficacy of tofacitinib in patients with active psoriatic arthritis: interim analysis of OPAL Balance, an open-label, long-term extension study. *Rheumatol Ther* 2020; **7**: 553–80.

14 Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010; **69**: 48–53.

15 Clegg DO, Reda DJ, Mejias E, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996; **39**: 2013–20.

16 Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol* 2008; **58**: 851–64.

17 Helliwell PS, FitzGerald O, Fransen J. Composite disease activity and responder indices for psoriatic arthritis: a report from the GRAPPA 2013 meeting on development of cutoffs for both disease activity states and response. *J Rheumatol* 2014; **41**: 1212–7.

18 Mease PJ, Woolley JM, Bitman B, Wang BC, Globe DR, Singh A. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. *J Rheumatol* 2011; **38**: 2461–5.

19 Burmester GR, Curtis JR, Yun H, et al. An integrated analysis of the safety of tofacitinib in psoriatic arthritis across phase III and long-term extension studies with comparison to real-world observational data. *Drug Saf* 2020; **43**: 379–92.

20 Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheumatol* 2016; **68**: 1060–71.

21 Behrens F, Koehm M, Schwaneck EC, et al. Addition or removal of concomitant methotrexate alters adalimumab effectiveness in rheumatoid arthritis but not psoriatic arthritis. *Scand J Rheumatol* 2019; **48**: 375–82.

22 Mease PJ, Collier DH, Saunders KC, Li G, Kremer JM, Greenberg JD. Comparative effectiveness of biologic monotherapy versus combination therapy for patients with psoriatic arthritis: results from the Corrona registry. *RMD Open* 2015; **1**: e000181.

23 Fagerli KM, Lie E, van der Heijde D, et al. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included

in the NOR-DMARD study. *Ann Rheum Dis* 2014; **73**: 132–7.

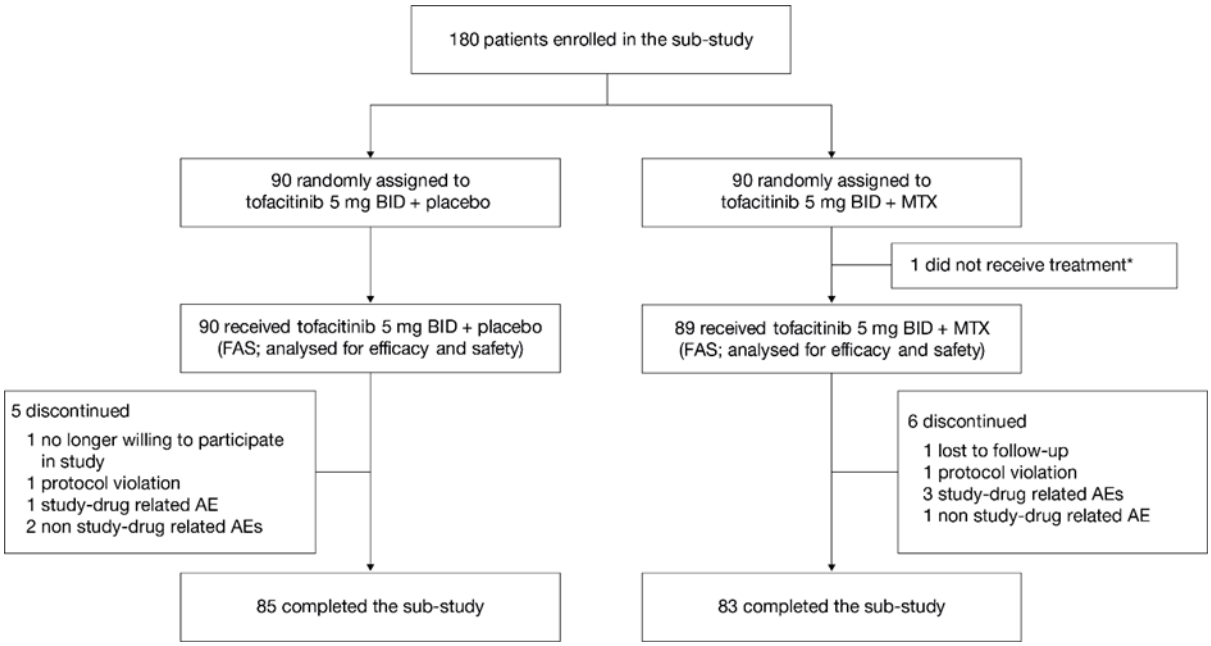
24 Cohen SB, Pope J, Haraoui B, et al. Methotrexate withdrawal in patients with rheumatoid arthritis who achieve low disease activity with tofacitinib modified-release 11 mg once daily plus methotrexate (ORAL Shift): a randomised, phase 3b/4, non-inferiority trial. *Lancet Rheumatol* 2019; **1**: E23–4.

25 Driessen RJ, de Jong EM, Salemink GW, Bürer JH, van de Kerkhof PC, van den Hoogen FH. Analysis of 4-year Dutch reimbursement application data of biological therapies for psoriatic arthritis. *Rheumatology (Oxford)* 2010; **49**: 588–91.

26 Kristensen LE, Gülfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. *Ann Rheum Dis* 2008; **67**: 364–9.

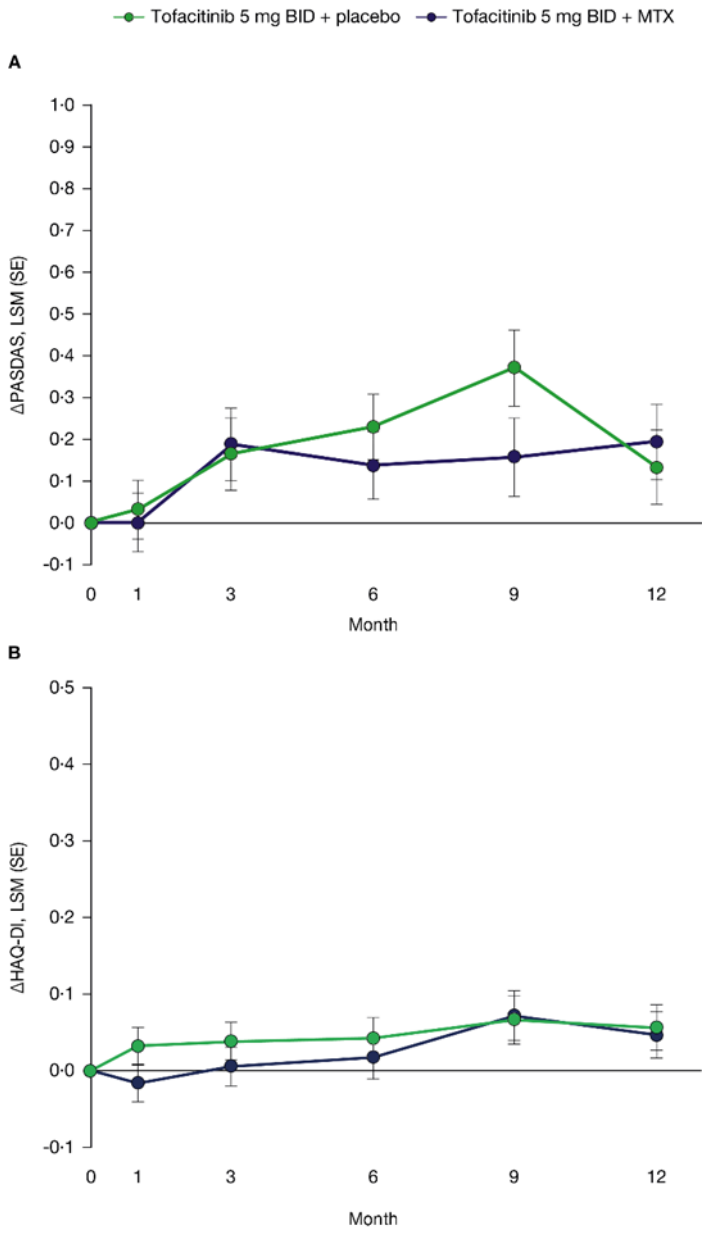
Figure legends

Figure 1: Patient disposition



AE=adverse event. BID=twice daily. FAS=full analysis set. MTX=methotrexate. *Patient was randomised in error.

Figure 2: **LSM (SE) change from sub-study baseline in (A) PASDAS[*] and (B) HAQ-DI[*] up to month 12**



For the LSM of continuous outcomes, the numbers of patients included in the repeated measures model from the tofacitinib 5 mg BID plus placebo and tofacitinib 5 mg BID plus methotrexate arms were 90 and 89, respectively. Δ=change from sub-study baseline. BID=twice daily. HAQ-DI=health assessment questionnaire-disability index. LSM=least squares mean. MTX=methotrexate. PASDAS=psoriatic arthritis disease activity score. SE=standard error. [*]Primary endpoint at month 6.

Table 1: **Patient demographics and sub-study baseline disease characteristics**

	Tofacitinib 5 mg BID plus placebo (N=90)	**Tofacitinib 5 mg BID plus methotrexate (N=89)**
Age, mean (SD), years	53·1 (11·0)	51·8 (11·4)
Female, n (%)	47 (52)	49 (55)
Race, n (%)		
White	87 (97)	83 (93)
Black	0	0
Asian	1 (1)	2 (2)
Other	2 (2)	4 (4)
Geographic region, n (%)		
United States	11 (12)	5 (6)
Australia and Western Europe	8 (9)	11 (12)
Russia and Eastern Europe	54 (60)	61 (69)
Rest of world	17 (19)	12 (13)
BMI, mean (SD), kg/m^2	30·5 (5·4)	30·0 (5·4)
Smoking classification, n (%)		
Never smoked	67 (74)	69 (78)
Smoker	11 (12)	9 (10)
Ex-smoker	12 (13)	11 (12)
Disease duration, mean (SD), years	11·3 (8·2)	11·2 (7·4)
PASDAS, mean (SD)	2·53 (1·24)	2·74 (1·23)
PASDAS, n (%)		
≤3·2 (LDA)	63 (70)	56 (63)
>3·2 to <5·4	25 (28)	32 (36)
≥5·4 (HDA)	2 (2)	1 (1)
HAQ-DI, mean (SD)	0·52 (0·58)	0·64 (0·67)
Presence of enthesitis,[*] n (%)	16 (18)	15 (17)
LEI,[†] mean (SD) [N1]	2·0 (1·3) [16]	1·4 (0·7) [15]
Presence of dactylitis,[‡] n (%)	1 (1)	7 (8)
TJC [68], mean (SD)	2·8 (4·3)	2·9 (3·6)

SJC [66], mean (SD)	0·5 (1·2)	0·8 (1·5)
PGA VAS, mean (SD), mm	9·2 (10·7)	11·8 (12·0)
Total psoriatic BSA,[§] mean (SD), % [N1]	4 (5) [42]	4 (5) [47]
PGA-PsO,[¶] mean (SD) [N1]	1·5 (0·7) [33]	1·4 (0·6) [41]
MDA, n (%)	53 (59)	41 (46)
PtGA VAS, mean (SD), mm	22·7 (20·6)	26·1 (22·0)
Pain VAS, mean (SD), mm	20·6 (20·3)	25·4 (21·6)
PGJS VAS,[**] mean (SD), mm	25·9 (22·3)	29·9 (24·5)
SF-36v2 PCS score, mean (SD)	45·5 (8·8)	43·7 (8·4)
SF-36v2 MCS score, mean (SD)	48·0 (10·4)	45·3 (9·7)
FACIT-F total score, mean (SD)	38·8 (10·3)	36·7 (10·5)
CRP, mean (SD), mg/L	5·0 (12·2)	3·3 (4·2)
CRP >2·87 mg/L, n (%)	35 (39)	28 (32)
RF+,[††] n (%)	7 (8)	8 (9)
Anti-CCP antibody+,[††] n (%)	6 (7)	7 (8)
Previous bDMARD use,[‡‡] n (%)	39 (43)	36 (40)
Baseline MTX dose, [§§] mean (SD), mg/week	15·3 (4·0)	14·6 (4·4)

bDMARD=biologic disease-modifying antirheumatic drug. BID=twice daily. BMI=body mass index. BSA=body surface area. CCP=cyclic citrullinated peptide. CRP=C-reactive protein. DSS=dactylitis severity score. FACIT-F=functional assessment of chronic illness therapy-fatigue. HAQ-DI=health assessment questionnaire-disability index. HDA=high disease activity. LDA=low disease activity. LEI=Leeds enthesitis index. LTE=long-term extension. MCS=mental component summary. MDA=minimal disease activity. N=number of patients randomised and treated. N1=number of patients meeting the baseline criteria. Pain=patient's assessment of arthritis pain. PASDAS=psoriatic arthritis disease activity score. PCS=physical component summary. PGA=physician global assessment of arthritis. PGA-PsO=physician global assessment of psoriasis. PGJS=patient's global joint and skin assessment. PtGA=patient global assessment of arthritis. RF=rheumatoid factor. SD=standard deviation. SF-36v2=short form-36 health survey (version 2, acute). SJC [66]=swollen joint count out of 66 joints. TJC [68]=tender/painful joint count out of 68 joints. TNFi=tumour necrosis factor inhibitor. VAS=visual analogue scale. [*]LEI >0. [†]In patients with LEI >0 at baseline. [‡]DSS >0. [§]In patients with total psoriatic BSA >0% at baseline. [¶]In patients with PGA-PsO >0 at baseline. [**]Global (psoriasis and arthritis; question: in all the ways in which your psoriasis and arthritis, as a whole, affects you, how would you rate the way you felt over the past week?). [††]Obtained from screening visit of qualifying study. [‡‡]Any TNFi or non-TNFi bDMARD taken before sub-study baseline (includes data collected from the qualifying study). [§§]Based on concomitant medication data recorded during the LTE study.

Table 2: **Secondary clinical efficacy and patient-reported outcomes at month 6 and month 12**

	Month 6			Month 12		
	Tofacitinib 5 mg BID plus placebo (N=90)	**Tofacitinib 5 mg BID plus methotrexate (N=89)**	**Treatment difference[*] (95% CI)**	**Tofacitinib 5 mg BID plus placebo (N=90)**	**Tofacitinib 5 mg BID plus methotrexate (N=89)**	**Treatment difference[*] (95% CI)**
ΔLEI,[†] LSM (SE) [N1]	-0·7 (0·3) [16]	-0·5 (0·3) [15]	-0·2 (-1·1, 0·6)	-0·3 (0·3) [16]	-0·5 (0·3) [15]	0·2 (-0·6, 1·0)
LEI,[‡] mean (SE) [N2]	0·2 (0·1) [72]	0·2 (0·1) [69]	··	0·1 (0·1) [70]	0·2 (0·1) [68]	··
Absence of enthesitis,[‡] n (%) [N2]	68 (94) [72]	63 (91) [69]	··	68 (97) [70]	62 (91) [68]	··
DSS,[§,¶] mean (SE) [N2]	0·0 (0·0) [87]	0·0 (0·0) [78]	··	0·0 (0·0) [84]	0·0 (0·0) [77]	··
Absence of dactylitis,[§] n (%) [N2]	87 (100) [87]	78 (100) [78]	··	83 (99) [84]	76 (99) [77]	··
ΔTJC [68], LSM (SE)	0·5 (0·4)	0·5 (0·4)	0·0 (-1·0, 1·0)	0·5 (0·3)	0·3 (0·3)	0·2 (-0·7, 1·1)
ΔSJC [66], LSM (SE)	0·1 (0·2)	0·1 (0·2)	0·0 (-0·4, 0·5)	0·0 (0·1)	0·1 (0·1)	-0·1 (-0·5, 0·3)
ΔPGA, LSM (SE), mm	1·7 (1·0)	1·2 (1·0)	0·5 (-2·3, 3·2)	0·8 (1·1)	0·9 (1·1)	-0·1 (-3·3, 3·0)
ΔCRP, LSM (SE), mg/L	-0·3 (0·8)	0·5 (0·8)	-0·8 (-3·0, 1·4)	0·3 (0·8)	-0·1 (0·8)	0·4 (-1·8, 2·5)
Percent ΔBSA,[**] LSM (SE), % [N1]	18 (21) [42]	42 (21) [46]	-24 (-83, 35)	42 (20) [42]	35 (20) [46]	7 (-50, 64)
ΔPGA-PsO,[††] LSM (SE) [N1]	0·2 (0·1) [33]	-0·1 (0·1) [41]	0·3 (0·0, 0·6)[‡‡]	0·3 (0·2) [33]	0·0 (0·2) [41]	0·3 (-0·1, 0·7)
MDA,[§§] n (%)	44 (49)	41 (46)	3 (-12, 17)	40 (44)	37 (42)	3 (-12, 17)
PsARC,[§§] n (%)	6 (7)	11 (12)	-6 (-14, 3)	3 (3)	12 (13)	-10 (-18, -2)[‡‡]

ΔPtGA VAS, LSM (SE), mm	4·5 (1·7)	3·2 (1·7)	1·3 (-3·5, 6·1)	2·7 (1·6)	2·8 (1·6)	0·1 (-4·6, 4·4)
ΔPain VAS, LSM (SE), mm	4·1 (1·7)	3·1 (1·7)	1·0 (-3·8, 5·7)	3·4 (1·7)	2·7 (1·7)	0·7 (-4·0, 5·4)
ΔPGJS VAS,[¶¶] LSM (SE), mm	1·8 (1·7)	-0·2 (1·7)	2·1 (-2·7, 6·8)	0·3 (1·8)	2·1 (1·8)	-1·9 (-6·9, 3·1)
ΔSF-36v2 PCS score, LSM (SE)	-1·4 (0·5)	-0·7 (0·5)	-0·8 (-2·1, 0·6)	-1·0 (0·5)	-1·5 (0·5)	0·5 (-1·0, 2·0)
ΔSF36v2 MCS score, LSM (SE)	-0·9 (0·7)	-0·2 (0·7)	-0·7 (-2·7, 1·4)	-0·5 (0·7)	-0·4 (0·7)	-0·1 (-2·0, 1·8)
ΔFACIT-F total score, LSM (SE)	-2·0 (0·6)	-1·3 (0·6)	-0·7 (-2·4, 1·0)	-0·7 (0·6)	-1·4 (0·7)	0·8 (-1·1, 2·6)
ΔEQ-VAS, LSM (SE), mm	-1·9 (1·4)	4·4 (1·4)	-6·3 (-10·2, -2·4)[‡‡]	-1·9 (1·8)	3·0 (1·8)	-4·9 (-9·9, 0·2)

For the LSM of continuous outcomes (except ΔLEI, percent ΔBSA, and ΔPGA-PsO), the numbers of patients included in the repeated measures model from the tofacitinib 5 mg BID plus placebo and tofacitinib 5 mg BID plus methotrexate arms were 90 and 89, respectively. Δ=change from sub-study baseline. BID=twice daily. BSA=body surface area. CI=confidence interval. CRP=C-reactive protein. DSS=dactylitis severity score. EQ=EuroQoL. FACIT-F=functional assessment of chronic illness therapy-fatigue. LEI=Leeds enthesitis index. LSM=least squares mean. MCS=mental component summary. MDA=minimal disease activity. N1=number of patients meeting the baseline criteria and included in the repeated measures model. N2=number of patients meeting the baseline criteria and evaluable at each visit. N=number of patients randomised and treated. N=number of patients with outcome. Pain=patient's assessment of arthritis pain. PCS=physical component summary. PGA=physician global assessment of arthritis. PGA-PsO=physician global assessment of psoriasis. PGJS=patient's global joint and skin assessment. PsARC=psoriatic arthritis response criteria. PtGA=patient global assessment of arthritis. SE=standard error. SF-36v2=short form-36 health survey (version 2, acute). SJC [66]=swollen joint count out of 66 joints. TJC [68]=tender/painful joint count out of 68 joints. VAS=visual analogue scale. [*]Tofacitinib 5 mg BID plus placebo - tofacitinib 5 mg BID plus methotrexate. Reported as LSM difference (95% CI) for continuous endpoints, and as proportion difference (95% CI) for binary endpoints (%). [†]In patients with LEI >0 at baseline. [‡]In patients with LEI=0 at baseline, no imputation. [§]In patients with DSS=0 at baseline, no imputation. [¶]LSM ΔDSS was not calculated due to the low number of patients with DSS >0 at baseline. [**]In patients with BSA >0% at baseline. [††]In patients with PGA-PsO >0 at baseline. [‡‡]95% CI of the treatment difference between tofacitinib 5 mg BID plus placebo and tofacitinib 5 mg BID plus methotrexate excluded 0. [§§]Missing response = non-response. [¶¶]Global (psoriasis and arthritis; question: in all the ways in which your psoriasis and arthritis, as a whole, affects you, how would you rate the way you felt over the past week?).

Table 3: **Summary of AEs and laboratory abnormalities up to month 12**

	Tofacitinib 5 mg BID plus placebo (N=90)	**Tofacitinib 5 mg BID plus methotrexate (N=89)**
Patients with AEs, n (%)	43 (48)	41 (46)
Patients with SAEs, n (%)	4 (4)	3 (3)
Patients with severe AEs, n (%)	2 (2)[*]	0
Patients who discontinued due to AEs, n (%)	3 (3)	4 (4)
Patients with dose reduction or who temporarily discontinued due to AEs, n (%)	7 (8)	5 (6)
Deaths, n (%)	0	0
Most common (≥3% of patients in either treatment arm) AEs by MedDRA PT, n (%)		
URTI	4 (4)	6 (7)
UTI	4 (4)	3 (3)
Bronchitis	3 (3)	2 (2)
Pharyngitis	3 (3)	3 (3)
Nasopharyngitis	3 (3)	1 (1)
Psoriatic arthropathy	1 (1)	3 (3)
Diarrhoea	3 (3)	0
Patients with AEs of special interest, n (%)		
All herpes zoster (non-serious and serious)[†]	1 (1)	2 (2)

Serious infections		0		2 (2)
Opportunistic infections‡		0		1 (1)§
Malignancies (excluding NMSC)‡		1 (1)¶		1 (1)**
NMSC‡		0		0
MACE‡		0		0
DVT††		0		0
PE††		0		0
ATE††		1 (1)‡‡		0
Gastrointestinal perforation‡		0		0
Interstitial lung disease§§		0		0
Patients with laboratory abnormalities,¶¶ n (%)				
ALT >1×ULN		28 (31)		42 (47)
ALT ≥2×ULN		2 (2)		10 (11)
ALT ≥3×ULN		0		5 (6)
AST >1×ULN		27 (30)		30 (34)
AST ≥2×ULN		1 (1)		7 (8)
AST ≥3×ULN		0		3 (3)
Laboratory parameters, mean (SE) [N1]	**Month 6**	**Month 12**	**Month 6**	**Month 12**
ΔANC, $10^3/mm^3$	0·1 (0·2) [87]	0·1 (0·2) [85]	-0·2 (0·2) [83]	-0·2 (0·2) [82]
ΔALC, $10^3/mm^3$	0·1 (0·0) [87]	0·1 (0·0) [85]	-0·1 (0·0) [83]	0·0 (0·0) [82]

ΔPlatelets, $10^3/mm^3$	-1·8 (5·5) [87]	14·0 (5·6) [84]	-9·6 (5·2) [82]	1·5 (4·9) [82]
ΔHaemoglobin, g/dL	-0·1 (0·1) [87]	0·2 (0·1) [85]	-0·3 (0·1) [83]	-0·1 (0·1) [83]
ΔCreatinine, mg/dL	0·0 (0·0) [88]	0·0 (0·0) [86]	0·0 (0·0) [83]	0·0 (0·0) [83]
ΔALT, IU/L	-3·0 (1·6) [88]	-2·7 (1·6) [86]	4·5 (2·1) [83]	2·5 (1·3) [83]
ΔAST, IU/L	-1·7 (1·1) [88]	-1·5 (1·2) [86]	3·1 (1·0) [83]	1·7 (0·8) [83]
ΔCK, U/L	-6·9 (14·4) [88]	4·7 (21·9) [86]	1·2 (11·0) [83]	-18·5 (9·4) [83]

Δ=change from sub-study baseline. AE=adverse event. ALC=absolute lymphocyte count. ALT=alanine aminotransferase. ANC=absolute neutrophil count. AST=aspartate aminotransferase. ATE=arterial thromboembolism. BID=twice daily. CK=creatine kinase. DVT=deep vein thrombosis. MACE=major adverse cardiovascular event. MedDRA=Medical Dictionary of Regulatory Activities. N1=number of patients evaluable at each visit and baseline. NMSC=non-melanoma skin cancer. PE=pulmonary embolism. PT=preferred term. SAE=serious adverse event. SE=standard error. ULN=upper limit of normal. URTI=upper respiratory tract infection. UTI=urinary tract infection. [*]One event of forearm fracture and one event of bladder cancer. [†]One serious event of pneumonia herpes viral was reported in a patient receiving tofacitinib 5 mg BID plus methotrexate; the other herpes zoster events were non-serious. [‡]Reviewed by an independent external adjudication committee. [§]One patient receiving tofacitinib 5 mg BID plus methotrexate reported an event of herpes zoster and an event of pneumonia herpes viral, both of which were adjudicated as opportunistic infections. [¶]One event of bladder cancer. [**]One event of Bowen's disease. [††]Based on standardised MedDRA query terms. [‡‡]One event of carotid occlusion (non-serious). [§§]Reviewed by an independent internal adjudication committee. [¶¶]In all patients, without regard to baseline abnormality.