Safety and efficacy of tofacitinib up to 48 months in patients with active psoriatic arthritis: final analysis of the OPAL Balance long-term extension study

Peter Nash, Laura C Coates, Dona Fleishaker, Alan J Kivitz, Philip J Mease, Dafna D Gladman, Oliver FitzGerald, Cunshan Wang, Joseph Wu, Ming-Ann Hsu, Sujatha Menon, Lara Fallon, Keith S Kanik

School of Medicine, Griffith University, Brisbane, QLD, Australia (P Nash FRACP); **Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK** (L C Coates PhD); **Pfizer Inc, Groton, CT, USA** (D Fleishaker BSN, C Wang PhD, J Wu PhD, M-A Hsu MPH, S Menon PhD, K S Kanik MD); **Department of Rheumatology, Altoona Center for Clinical Research, Duncansville, PA, USA** (A J Kivitz MD); **Swedish Medical Center/Providence St Joseph Health and University of Washington, Seattle, WA, USA** (P J Mease MD); **Department of Medicine, University of Toronto and Krembil Research Institute, Toronto Western Hospital, Toronto, ON, Canada** (D Gladman MD); **Conway Institute for Biomolecular Research, School of Medicine, University College Dublin, Dublin, Ireland** (O FitzGerald MD); **Pfizer Inc, Montreal, QC, Canada** (L Fallon PhD)

Correspondence to:

Dona Fleishaker BSN, 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

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Research in context

Evidence before this study

We conducted a PubMed search (with no date restrictions) of English language publications reporting clinical trials of tofacitinib in patients with psoriatic arthritis (PsA). The search used the terms ((“tofacitinib” [All Fields] OR “tofacitinib” [MeSH Terms]) AND (“psoriatic arthritis” [All Fields] OR “arthritis, psoriatic” [MeSH Terms]) AND (Clinical Trial [Publication Type] OR Long-term extension [All Fields])). We identified one relevant publication; an interim analysis of the OPAL Balance long-term extension (LTE) study (NCT01976364), which reported data up to 36 months.

Added value of this study

To our knowledge, OPAL Balance is the longest clinical study of tofacitinib for the treatment of patients with active PsA. Overall, 66% of patients completed the 36-month LTE study or its 12-month methotrexate withdrawal sub-study (if enrolled). The safety and efficacy findings of this final analysis of data from OPAL Balance (reported up to 48 months [including sub-study data], and 36 months [excluding sub-study data], respectively) were consistent with those of the latest interim analysis (reported up to 36 and 30 months, respectively) and the qualifying phase 3 trials of the LTE study: no new or unexpected safety risks or laboratory parameter changes were observed and efficacy was maintained.

Implications of all the available evidence

As PsA is a chronic condition, it is important for the long-term efficacy and safety profiles of PsA therapies to be defined. Controlled studies of tofacitinib for PsA had demonstrated its efficacy and safety up to 12 months; however, long-term data were limited. The findings of this final analysis of the OPAL Balance LTE study show that the long-term safety profile (up

to 4 years) of tofacitinib in PsA is consistent with that of the phase 3 trials, and that efficacy was maintained over the 3 years of follow-up among patients remaining in the trial, supporting the use of tofacitinib for the long-term treatment of active PsA.

Summary

Background Tofacitinib is an oral Janus kinase inhibitor for the treatment of psoriatic arthritis (PsA). We report the final analysis of OPAL Balance, a 36-month long-term extension (LTE) study, with a 12-month methotrexate withdrawal sub-study, that assessed tofacitinib safety, tolerability, and efficacy in patients with active PsA.

Methods Eligible patients had participated in OPAL Broaden or Beyond phase 3 studies. Patients received open-label tofacitinib 5 mg twice daily (BID), with increases to 10 mg BID (for inadequate symptom control) and subsequent reductions to 5 mg BID (for safety) allowed from month 1. Certain conventional synthetic disease-modifying antirheumatic drugs could be continued concomitantly. Primary endpoints included incidence/severity of adverse events (AEs) and laboratory abnormalities, and laboratory parameter changes from baseline. Eligible LTE participants could enter the randomised, double-blind, sub-study (open-label tofacitinib 5 mg BID plus either blinded placebo or blinded methotrexate); safety data from which are included here (to month 48). Efficacy was reported to month 36 (sub-study excluded). OPAL Balance is complete and registered with ClinicalTrials.gov (NCT01976364).

Findings Between 17/02/2014–20/05/2019, 686 patients received tofacitinib 5 or 10 mg BID (179 patients treated in sub-study; 66·0% completed LTE/sub-study; mean treatment duration 794·6 days in LTE, 879·0 days in LTE/sub-study). To month 48, incidence of AEs, serious AEs, and discontinuations due to AEs was 83·7%, 16·8%, and 11·4%, respectively. Six patients died, one within the dosing risk period (incidence rate [IR; patients with events/100 patient-years]: 0·1). IRs for AEs of special interest included: herpes zoster (non-serious and serious), 1·7; serious infections, 1·0; opportunistic infections, 0·4; malignancies (excluding non-melanoma skin cancer [NMSC]), 0·7; NMSC, 0·9; major adverse cardiovascular events, 0·2; pulmonary embolism, 0·1; arterial thromboembolism, 0·4. No deep vein thromboses

occurred. Laboratory parameter changes were as expected with treatment. Efficacy was sustained through month 36.

Interpretation This analysis supports the long-term safety (48 months) and efficacy (36 months) of tofacitinib in patients with PsA, which were consistent with prior phase 3 studies.

Funding Pfizer Inc

Keywords Psoriatic Arthritis; Tofacitinib

Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease with musculoskeletal (eg, peripheral arthritis, dactylitis, enthesitis, and spondylitis) and dermatologic (eg, skin psoriasis) manifestations.[1–3] Patients usually require long-term treatment, with disease-modifying antirheumatic drugs (DMARDs), the mainstay pharmacological therapy. DMARDs, once limited to conventional synthetic DMARDs (csDMARDs, eg, methotrexate), now include targeted biologic (b)DMARDs with various mechanisms of action (eg, inhibition of tumour necrosis factor [TNF] or interleukin [IL]-12/23, IL-23-p19, or IL-17A/F), and targeted synthetic DMARDs that inhibit phosphodiesterase-4 or Janus kinases (JAKs).[3–9]

Given the chronic nature of PsA, it is important to determine the efficacy and safety profiles of PsA therapies—usually established in randomised controlled trials (RCTs) of relatively limited duration—over prolonged treatment periods. Long-term extension (LTE) studies provide an opportunity to evaluate long- and short-latency safety events and efficacy maintenance.

Tofacitinib is an oral JAK inhibitor for the treatment of PsA. Two phase 3 RCTs demonstrated the efficacy and safety of tofacitinib 5 or 10 mg twice daily (BID) in combination with a csDMARD for 12 or 6 months in patients with PsA with an inadequate response to ≥1 csDMARD and who were naive to TNF inhibitor (TNFi) therapy (OPAL Broaden, NCT01877668),[10] or who had an inadequate response to ≥1 TNFi (OPAL Beyond, NCT01882439).[11] Eligible patients from these studies could continue to receive open-label tofacitinib (with or without a csDMARD) in the LTE study OPAL Balance (NCT01976364), which examined the longer-term safety, tolerability, and efficacy of tofacitinib. In an OPAL Balance interim analysis of up to 36 months,[12] tofacitinib had a safety profile consistent with

that of the qualifying trials and maintained efficacy outcomes. Here, we present data from the completed OPAL Balance study, providing the final analysis of safety (up to 48 months) and efficacy (up to 36 months).

Methods

Methods for OPAL Balance and its sub-study have been reported previously[12,13] and are summarised here.

Study design and patients

OPAL Balance[12] was a 36-month, phase 3, LTE study (124 centres, 16 countries) that included patients who had participated in OPAL Broaden[10] or OPAL Beyond[11] (appendix p 6). All patients in OPAL Balance received open-label tofacitinib 5 mg BID; from month 1 onwards, the dose could be increased to 10 mg BID for inadequate PsA symptom control, and reduced to 5 mg BID for safety reasons thereafter. Select csDMARDs, administered per local standard-of-care, could be continued concomitantly. OPAL Balance included a 12-month, randomised, double-blind, methotrexate withdrawal sub-study (50 centres, 14 countries), in which patients received open-label tofacitinib 5 mg BID plus either blinded placebo or blinded methotrexate. Safety data from the sub-study are included in this final analysis (appendix p 6); efficacy data from the sub-study were excluded and reported elsewhere,[13] as they addressed methotrexate withdrawal, rather than maintenance of efficacy.

Inclusion and exclusion criteria for the qualifying trials have been detailed previously.[10,11] Briefly, eligible patients were adults (aged ≥18 years; ≥20 years in Taiwan) diagnosed with PsA ≥6 months previously, with active arthritis and plaque psoriasis. Patients could enter OPAL Balance ≤3 months after completing one of these studies or discontinuing for reasons other than study drug-related adverse events (AEs). Those who enrolled into the LTE study

>14 days after the qualifying trial final visit must have had sufficient PsA disease activity to warrant tofacitinib use. Detailed inclusion and exclusion criteria for the OPAL Balance LTE study are included in the appendix (pp 1–4). LTE study participants who received tofacitinib for ≥24 months (stable at 5 mg BID ≥3 months) and stable-dose oral methotrexate (7·5–20 mg/week) for ≥4 weeks could enter the sub-study. There were no PsA disease activity requirements for sub-study entry.

This analysis included data from the OPAL Balance final locked database (study start, 17/02/2014; study end, 20/05/2019; database release, 31/07/2019).

OPAL Balance was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, 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. An independent Data Safety Monitoring Board, external to the study sponsor, reviewed safety data on a cumulative basis, and Safety Endpoint Adjudication Committees provided standardised safety assessment for selected events. All patients provided written informed consent.

Objectives and endpoints

The primary objective of OPAL Balance was to evaluate the long-term safety and tolerability of tofacitinib in adult patients with active PsA.

Primary endpoints included AE incidence and severity, incidence of clinical laboratory abnormalities, and changes from baseline in laboratory parameters, up to month 48 in patients from the LTE study and sub-study (appendix p 5). Patients could enter the 12-month sub-

study between months 24 and 36 of the LTE study, giving a maximum treatment duration of 48 months.

Secondary and other endpoints were reported up to month 36 (ie, LTE study end). Rheumatological and dermatological secondary endpoints included: rates of response, as per American College of Rheumatology ≥20%, ≥50%, or ≥70% response criteria (ACR20, ACR50, and ACR70), Psoriatic Arthritis Response Criteria (PsARC), Psoriasis Area and Severity Index 75% improvement (PASI75; assessed in patients with plaque psoriasis affecting ≥3% of body surface area at baseline and with a baseline PASI score >0), and changes from baseline in Physician Global Assessment of Psoriasis (PGA-PsO; assessed in patients with baseline PGA-PsO >0), Leeds Enthesitis Index (LEI; assessed in patients with baseline LEI >0), and Dactylitis Severity Score (DSS; assessed in patients with baseline DSS >0). Composite other endpoints included: minimal disease activity (MDA) and very low disease activity (VLDA) (post hoc endpoint) achievement rates, and changes from baseline in Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriasis Disease Activity Index (CPDAI; assessed in patients with plaque psoriasis affecting ≥3% of body surface area at baseline), and Psoriatic Arthritis Disease Activity Score (PASDAS). Patient-reported outcomes (PROs; secondary endpoints unless specified as other) included: Health Assessment Questionnaire-Disability Index (HAQ-DI) response rates (assessed in patients with baseline HAQ-DI ≥0·35; other endpoint) and changes from baseline in HAQ-DI, Patient Assessment of Arthritis Pain (Pain; visual analogue scale [VAS] 0–100 mm; other endpoint), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) total score, Dermatology Life Quality Index (DLQI; other endpoint), Short Form-36 Health Survey version 2 (SF-36v2) Physical and Mental Component Summary (PCS and MCS) scores and norm-based domain scores, and EuroQoL-Five Dimensions-Three Level Health Questionnaire (EQ-5D-3L) scores and EQ-VAS (‘Your own health state today’; VAS 0–100 mm).

Statistical analysis

Given the open-label study design, no formal hypothesis testing was conducted. The safety analysis set included patients who received ≥1 tofacitinib dose in OPAL Balance, reporting cumulative safety data from the LTE study plus sub-study. The efficacy analysis set also included patients who received ≥1 tofacitinib dose in OPAL Balance, but reported only data from the main LTE study (ie, up to month 36). The main analysis group for both efficacy and safety analyses was the all tofacitinib group (ie, all patients who received ≥1 dose of tofacitinib in OPAL Balance). Missing values were not imputed; only observed values were used.

Potential dose-related effects were assessed post hoc in three additional analysis groups: average tofacitinib 5 mg BID, average tofacitinib 10 mg BID, and constant tofacitinib 5 mg BID. Assignment to these groups was based on overall tofacitinib exposure in the LTE study (to 36 months), plus the sub-study if the patient enrolled (up to 48 months). Average total daily dose (ATDD) was the sum total daily doses of tofacitinib received (in mg) divided by the total number of treatment days during this study. Patients were assigned to either the average tofacitinib 5 mg or 10 mg BID group based on whether the ATDD was <15 mg or ≥15 mg, respectively. The constant tofacitinib 5 mg BID group included only patients who started and stayed on tofacitinib 5 mg BID, until switching to tofacitinib 10 mg BID or discontinuing the study. Only data up to the last dose of constant tofacitinib 5 mg BID dosing were included (data after switching to 10 mg BID were excluded). The constant tofacitinib 5 mg BID group was therefore a subset of the all tofacitinib group and not exclusive of the two average tofacitinib groups.

Patient demographics, baseline disease characteristics, and baseline values for efficacy or PROs were obtained from the qualifying study baseline. Baseline values for safety endpoints

came from the qualifying study or from OPAL Balance, for patients enrolled ≤14 days or >14 days after qualifying study final visit, respectively.

Incidence rates (IRs; patients with events per 100 patient-years [PY] of exposure) were estimated for selected safety outcomes based on events during the risk period, predefined as the time from treatment exposure to the last dose plus 28 days or date of last observation, whichever was earlier.[12] This approach enabled the risk of developing an event during the treatment and immediate post-treatment (up to 28 days) periods to be quantified, and differing follow-up times to be accounted for. The 95% confidence intervals (CIs) were calculated based on Exact Poisson distribution. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

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

Role of the funding source

This study was sponsored by Pfizer Inc. 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. The authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

In OPAL Balance, 686 patients received tofacitinib and were included in the all tofacitinib group for efficacy and safety analyses. At study end (20/05/2019), 453 (66·0%) had completed and 233 (34·0%) had discontinued either the LTE study or the methotrexate withdrawal sub-study (if enrolled; figure 1). Of the 180 patients screened for the sub-study, all were randomised, and 179 were treated (90 tofacitinib monotherapy, 89 tofacitinib plus methotrexate) and included in the safety analyses here.

In the all tofacitinib group, the mean (standard deviation [SD]) and total duration of tofacitinib treatment was 794·6 (329·2) days and 1492·4 PY (appendix pp 19–20), respectively, in the LTE study. The mean (SD) and total duration of tofacitinib treatment in the LTE study plus sub-study (ie, cumulative exposure) was 879·0 (396·6) days and 1651·0 PY, respectively.

The most common reasons for discontinuation included AEs (n=78, 11·4%), no longer being willing to participate (n=70, 10·2%), and insufficient clinical response (n=40, 5·8%) (figure 1).

Demographics/baseline characteristics are reported in the appendix (pp 19–20). In the all tofacitinib group, the mean (SD) PsA duration was 7·6 (7·2) years. At baseline, 674 (98·3%) patients were receiving concomitant csDMARDs, most commonly methotrexate, and 132 (19·2%) were receiving concomitant oral corticosteroids. The proportion of patients receiving concomitant oral corticosteroids was numerically lower in the average tofacitinib 10 mg BID group than the other tofacitinib groups. Of the 686 OPAL Balance participants, 21 (3·1%) enrolled >14 days after the qualifying study final visit; safety endpoint baseline values for these patients were from the LTE screening visit.

Up to month 48, 574 (83·7%) patients in the all tofacitinib group reported all-causality AEs, 86 (12·5%) reported severe AEs, 115 (16·8%) experienced serious AEs (SAEs), 78 (11·4%) discontinued due to AEs, and 243 (35·4%) had their tofacitinib dose reduced or temporarily discontinued due to AEs.

In the all tofacitinib group, the IR (95% CI) per 100 PY was 6·9 (5·7–8·4) for SAEs and 3·3 (2·5–4·3) for discontinuations due to AEs (table 1). IRs for SAE were similar across treatment groups; however, the IR for discontinuations due to AEs in the average tofacitinib 10 mg BID group was numerically lower than the average tofacitinib 5 mg BID group (table 1). The most

common AEs in the all tofacitinib group included upper respiratory tract infection and nasopharyngitis (both occurring in >10% of patients; appendix p 21).

In the all tofacitinib group, six deaths occurred up to month 48, of which five were after the 28-day risk period; the IR for the one death within the risk period (due to chronic obstructive pulmonary disease; appendix p 22) was 0·1 (0·0–0·3) per 100 PY (table 1). Causes of death outside the risk period included acute cardiac failure/hypertensive heart disease, cardiovascular insufficiency, metastatic pancreatic carcinoma, pulmonary embolism (PE), and chemical poisoning/hepatic failure (appendix p 22).

IRs for AEs of special interest are reported in table 1. For all herpes zoster (HZ; non-serious and serious), the IR (95% CI) was 1·7 (1·2–2·5) per 100 PY in the all tofacitinib group and was generally similar among the other groups. HZ occurred only within the risk period, with one case considered to be serious in the 29 patients affected; the case resolved after tofacitinib discontinuation. HZ was adjudicated as an opportunistic infection in six patients; one had multidermatomal HZ, two had disseminated HZ, two had both multidermatomal and disseminated HZ, and one had HZ in two adjacent dermatomes (plus pneumonia herpes viral, likewise adjudicated as an opportunistic/special interest infection). Serious infections occurred only within the risk period; the IR (95% CI) was 1·0 (0·6–1·6) per 100 PY in the all tofacitinib group and was generally similar across the other treatment groups. There were no reports of active tuberculosis (six patients reported latent tuberculosis as a treatment-emergent AE) or adjudicated gastrointestinal perforations. One patient in the all tofacitinib group reported interstitial lung disease; IR (95% CI) was 0·1 (0·0–0·3) per 100 PY.

In the all tofacitinib group, the IR (95% CI) was 0·7 (0·4–1·2) per 100 PY for adjudicated malignancies (excluding non-melanoma skin cancer [NMSC]) and 0·9 (0·5–1·5) per 100 PY for NMSC (table 1). Across the other groups, the corresponding IRs were generally similar,

although the IR for malignancies (excluding NMSC) was numerically lower in the average tofacitinib 10 mg BID than in the average tofacitinib 5 mg BID group.

For adjudicated major adverse cardiovascular events (MACE), the IR (95% CI) was 0·2 (0·1–0·6) per 100 PY in the all tofacitinib group; this was generally similar across the other groups. Of the four MACE within the risk period in the all tofacitinib group, one was fatal. Two MACE occurred outside the risk period, each fatal.

The PE IR (95% CI) was 0·1 (0·0–0·3) in the all tofacitinib group. The one PE within the risk period was non-fatal and occurred in a 66-year-old White male included in both the average tofacitinib 5 mg BID and constant tofacitinib 5 mg BID groups, who had received tofacitinib 10 mg BID previously in OPAL Broaden. The patient was noted to have several cardiovascular/venous thromboembolism risk factors (aged ≥60 years, male, body mass index ≥30 kg/m^2, baseline C-reactive protein >2·87 mg/L, and hypertension) and also had two brothers who had died from PE (although coagulopathy disorders had not been investigated in the brothers or the patient). The one PE outside the risk period was fatal. The patient was a 45-year-old White female included in the average tofacitinib 5 mg BID and constant tofacitinib 5 mg BID groups, who had received tofacitinib 5 mg BID previously in OPAL Beyond. The patient was obese and had lower leg peripheral oedema.

All arterial thromboembolism (ATE) events occurred within the risk period; the IR (95% CI) was 0·4 (0·1–0·8) in the all tofacitinib group. There were no reports of deep vein thrombosis (DVT).

Although not an AE of special interest, it is relevant to note that one patient (average tofacitinib 5 mg BID group) reported Crohn's disease within the risk period.

The proportions of patients who experienced liver parameter elevations are reported in the appendix (p 23). In the all tofacitinib group, 36 (5·3%) patients had alanine aminotransferase (ALT) elevated ≥3 × upper limit of normal (ULN), 22 (3·2%) had aspartate aminotransferase (AST) elevated ≥3 × ULN, and 17 (2·5%) had gamma glutamyl transferase elevated ≥5 × ULN. No dose response was evident across the average tofacitinib 5 and 10 mg BID groups.

Laboratory parameter changes met discontinuation criteria in 9 (1·3%) patients in the all tofacitinib group, and in 4 (1·0%), 5 (1·8%), and 4 (0·6%) patients in the average tofacitinib 5 mg BID, average tofacitinib 10 mg BID, and constant tofacitinib 5 mg BID groups, respectively (appendix p 24). The discontinuation criteria most commonly met were those of two sequential AST or ALT elevations ≥5 × ULN regardless of total bilirubin or accompanying signs or symptoms, which occurred in 3 (0·4%) patients in the all tofacitinib group. No patients met the criteria of two sequential absolute neutrophil counts (ANC) <1·0 × $10^3/mm^3$ or that of two sequential creatine kinase elevations >10 × ULN.

Changes from baseline in laboratory parameters over 48 months generally followed a similar trend in each treatment group (figure 2 and appendix pp 7–8). Changes in ALT, AST, absolute lymphocyte count (ALC), ANC, and creatine kinase remained relatively stable following an initial increase (ALT, AST, creatine kinase) or decrease (ANC), with ALC increasing from baseline to month 1, then decreasing to month 24 before stabilising (figure 2). Small and transient increases were observed in lipid parameters (appendix pp 7–8). Changes in certain laboratory parameters, including ALC, creatine kinase, haemoglobin, low-density lipoprotein cholesterol, and total cholesterol, appeared to be more pronounced in the average tofacitinib 10 mg BID group than in the average tofacitinib 5 mg BID or constant tofacitinib 5 mg BID groups. Absolute mean laboratory parameter values are reported in appendix pp 9–10.

Efficacy

Among patients who remained in the LTE study, rates of ACR20, ACR50, ACR70, and PsARC response, were maintained to month 36 across all treatment groups (figure 3).

Similarly, improvements in psoriasis, including PASI75 response rates (figure 3) and changes from baseline in PGA-PsO (appendix p 11) were maintained over time in each treatment group, as were improvements from baseline in LEI and DSS (appendix p 11).

In the all tofacitinib group, 233 (34·6%) patients had MDA and 69 (10·3%) had VLDA at month 1; these rates were maintained to month 36 (appendix pp 12–13). Overall, improvements from baseline in DAPSA, CPDAI, and PASDAS, were maintained to month 36 across all treatment groups (appendix pp 12–13).

Across treatment groups, PRO measures were generally maintained to month 36, including: HAQ-DI response rate, and improvements from baseline in HAQ-DI; Patient Assessment of Arthritis Pain; FACIT-F total score; DLQI; SF-36v2 PCS and MCS scores (appendix pp 14–15; SF-36v2 norm-based domain scores (appendix p 16); EQ-5D-3L scores; and EQ-VAS scores (appendix pp 17–18).

Notably, efficacy generally appeared to be less pronounced in the average tofacitinib 10 mg BID group than in the average tofacitinib 5 mg BID and constant tofacitinib 5 mg BID groups, as measured by the proportion of patients achieving ACR20, ACR50, ACR70, PsARC, and PASI75 responses, MDA, and VLDA, as well as changes from baseline in certain clinical outcomes (PGA-PsO, DAPSA, CPDAI, PASDAS) and PROs (FACIT-F total score, DLQI, and SF-36v2 PCS and MCS). These efficacy differences were particularly evident during the first 21–24 months of the LTE study, although were largely sustained through to month 36 for MDA and VLDA.

Discussion

This final analysis of the OPAL Balance LTE study provides safety (up to 48 months, including sub-study safety data) and efficacy (up to 36 months) data for tofacitinib, representing the longest time period of any tofacitinib clinical study for active PsA to date. Around two-thirds of participants completed the study, indicating a good degree of persistence with tofacitinib therapy up to 4 years.

The safety profile of tofacitinib in this analysis was generally similar to that seen in the interim analysis of the study (which assessed AEs and laboratory abnormalities up to 36 months, and changes from baseline in laboratory parameters up to 30 months),[12] and the qualifying studies (6-month OPAL Broaden;[10] 12-month OPAL Beyond[11]).

By month 48, 83·7% of patients in the all tofacitinib group had reported AEs, most commonly upper respiratory tract infection and nasopharyngitis, reflecting the findings of the qualifying studies,[10,11] the OPAL Balance interim analysis,[12] and the long-term (up to 9·5 years) global LTE study of tofacitinib in rheumatoid arthritis (RA).[14] IRs for SAEs and discontinuations due to AEs in the all tofacitinib group were 6·9 and 3·3 per 100 PY, respectively. IRs for SAEs were generally consistent across the individual dose groups (ie, average tofacitinib 5 mg BID, average tofacitinib 10 mg BID, and constant tofacitinib 5 mg BID), whereas the IR for discontinuations due to AEs was numerically lower with average tofacitinib 10 mg BID versus 5 mg BID, a finding potentially impacted by the differing proportions of patients receiving concomitant oral corticosteroids in these two groups.

Six deaths occurred in the all tofacitinib group versus five in the interim analysis,[12] with the additional death due to chemical poisoning/hepatic failure occurring outside the risk period.

In this final analysis, the exposure-adjusted IRs for AEs of special interest, including HZ, serious infections, opportunistic infections, malignancies (excluding NMSC), NMSC, MACE, PE, and ATE, were consistent with those reported in the interim analysis,[12] suggesting that there was no increase in risk over time. No DVT, active tuberculosis, or gastrointestinal perforations had occurred in the study by month 48. IRs for DVT, PE and ATE in this final LTE analysis are consistent with those from a previous analysis of pooled OPAL Broaden, OPAL Beyond, and OPAL Balance data.[15] A recent, evidence-based consensus statement on JAK inhibitor use advises that risk factors for venous thromboembolism are to be considered before initiating JAK inhibitor treatment.[16]

The long-term safety profile of tofacitinib in OPAL Balance appears to be generally consistent with that of bDMARDs,[17-22] with HZ rates among the potential points of difference.[12] When pooled data from OPAL Broaden, OPAL Beyond, and the OPAL Balance interim analysis were recently compared with observational data for other PsA therapies (csDMARDs, bDMARDs, or apremilast), tofacitinib displayed a safety profile largely consistent with that of the other treatments, albeit with the IR for HZ being 2·0–2·7 per 100 PY across the tofacitinib cohorts versus 0·8–2·0 per 100 PY with the other treatments, in line with HZ being a known risk for tofacitinib.[23]

Overall, laboratory parameter changes in this analysis were as expected with tofacitinib treatment. Similar to long-term findings with tofacitinib in patients with RA,[24] ALC in OPAL Balance increased from baseline to month 1, then declined to month 24. Changes generally stabilised thereafter, with one patient meeting the study discontinuation criteria of two sequential ALC measurements $<0{\cdot}5 \times 10^3/mm^3$. Lymphocyte monitoring is recommended in the tofacitinib prescribing information, as infection risk may be higher with increasing degrees of lymphopenia.[25,26] CD16+56 lymphocyte (ie, natural killer cell) levels fluctuated in

OPAL Balance, although an analysis of tofacitinib clinical trials in patients with RA generally found no strong associations between lymphocyte levels, including natural killer cells, and serious infections.[24]

Tofacitinib has been associated with an increased likelihood of liver enzyme elevations, particularly in studies involving concomitant csDMARD therapy, often methotrexate,[25] which is known to carry a hepatotoxicity risk in patients with PsA.[4,27] Liver enzyme elevations were observed with tofacitinib in this analysis, although in the sub-study, the proportion of patients who experienced elevations with tofacitinib appeared greater with continued methotrexate use than after methotrexate withdrawal.[13]

Finally, of interest, small and transient increases were observed in lipid parameters.

The efficacy of tofacitinib in OPAL Broaden[10] and OPAL Beyond[11] was maintained to 36 months in the patients who remained in OPAL Balance, with the efficacy findings of this final analysis being generally consistent with those of the interim analysis.[12] In general, efficacy appeared to be less pronounced in the average tofacitinib 10 mg BID group than in the average tofacitinib 5 mg BID and constant tofacitinib 5 mg BID groups, particularly during the first 21–24 months of the LTE study. Selection bias may have contributed to this finding, as only patients with inadequate symptom control were offered the 10 mg BID dose as per protocol, indicating that this population may be more refractory to tofacitinib treatment. However, the study was not designed to compare doses.

Various limitations require consideration when interpreting the final OPAL Balance analysis. Most participants were known to have responded to, and tolerated, tofacitinib (all had completed a qualifying study), the LTE study was open-label and had no placebo group , analyses used observed values, and assessments of dose-related effects were conducted post hoc. There are also inherent limitations to the algorithms used to evaluate dose-related effects.

These include, for ATDD, a possible difference between the dose category the patient is assigned to and the actual dose at which an AE occurs (as a patient is assigned to a single dose category), and a narrowing of the differences between point estimates for both doses, which could make the differences more difficult to evaluate. For the constant daily dose algorithm, limitations include a shorter overall tofacitinib exposure and the potential for findings to be confounded by the reasons for discontinuations or dose changes (as exposure and events that occur after a dose switch are excluded).

In conclusion, the safety (up to 48 months) and efficacy (up to 36 months) of tofacitinib in this final analysis of OPAL Balance were consistent with those of the interim analysis and qualifying trials, with no new or unexpected safety risks or laboratory parameter changes, and efficacy being maintained in patients who remained in the LTE study. These data support the use of tofacitinib in the long-term treatment of active PsA.

Contributors

PN, DF, AJK, PJM, CW, JW, M-AH, SM, and KSK contributed to the conception/design of the study, acquisition of the data, and data analysis. All authors had access to the data, and PN and JW accessed and verified the data reported in this manuscript. All authors contributed to the interpretation of the data, critically revised each draft of the manuscript for intellectual content, provided final approval of the version submitted for publication, and accept accountability for the accuracy and integrity of the work.

Declaration of interests

PN has received research grants from, is a consultant for, 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.

LCC has received honoraria from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Eli Lilly, Medac, Novartis, Pfizer Inc, and UCB; and has received grants and/or consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, and Pfizer Inc.

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

AJK has received consulting fees from Boehringer Ingelheim, Flexion, Gilead, Pfizer Inc, Regeneron, Sanofi, and SUN Pharma Advanced Research; is a member of the speakers' bureau for AbbVie, Celgene, Eli Lilly, Flexion, Genzyme, Merck, Novartis, Pfizer Inc, and Sanofi; is an advisory committee/review panel member for Janssen; and is a shareholder of Gilead, GSK, Novartis, Pfizer Inc, and Sanofi. Altoona Center for Clinical Research, PC, at which AJK is employed, received financial support for participating in this clinical research trial.

PJM has received research grants and/or 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, Janssen, Novartis, Pfizer Inc, and UCB.

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

2 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.

3 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.

4 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.

5 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.

6 Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2020; **395**: 1126–36.

7 Deodhar A, Helliwell PS, Boehncke WH, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2020; **395**: 1115–25.

8 Ritchlin CT, Kavanaugh A, Merola JF, et al. Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2020; **395**: 427–40.

9 Mease PJ, Kellner H, Morita A, et al. OP0307 Efficacy and safety of risankizumab, a selective il-23p19 inhibitor, in patients with active psoriatic arthritis over 24 weeks: results from a phase 2 trial. *Ann Rheum Dis* 2018; **77 (suppl 2)**: 200–1 (abstr OP0307).

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

11 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.

12 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.

13 Nash P, Mease PJ, Fleishaker D, et al. 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. *Lancet Rheumatol* 2020; **Epub ahead of print**.

14 Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. *Arthritis Res Ther* 2019; **21**: 89.

15 Mease P, Charles-Schoeman C, Cohen S, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. *Ann Rheum Dis* 2020; **79**: 1400–13.

16 Nash P, Kerschbaumer A, Dorner T, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis* 2020; **Epub ahead of print**.

17 Mease PJ, Ory P, Sharp JT, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Ann Rheum Dis* 2009; **68**: 702–9.

18 Burmester GR, Mease P, Dijkmans BAC, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann Rheum Dis* 2009; **68**: 1863–9.

19 Kavanaugh A, Mease PJ, Reimold AM, et al. Secukinumab for long-term treatment of psoriatic arthritis: a two-year followup from a Phase III, randomized, double-blind placebo-controlled study. *Arthritis Care Res (Hoboken)* 2017; **69**: 347–55.

20 Curtis JR, Mariette X, Gaujoux-Viala C, et al. Long-term safety of certolizumab pegol in rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis and Crohn's disease: a pooled analysis of 11 317 patients across clinical trials. *RMD Open* 2019; **5**: e000942.

21 Deodhar A, Mease PJ, McInnes IB, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Res Ther* 2019; **21**: 111.

22 Kavanaugh A, McInnes IB, Mease P, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). *Ann Rheum Dis* 2014; **73**: 1689–94.

23 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.

24 van Vollenhoven R, Lee EB, Strengholt S, et al. Evaluation of the short-, mid-, and long-term effects of tofacitinib on lymphocytes in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2019; **71**: 685–95.

25 Pfizer Inc. Xeljanz® (tofacitinib): highlights of prescribing information. 2020. http://labeling.pfizer.com/ShowLabeling.aspx?id=959 (accessed December 8, 2020).

26 European Medicines Agency. XELJANZ (tofacitinib): summary of product characteristics. 2019. https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf (accessed December 8, 2020).

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

Figure legends

Figure 1: Patient disposition at completion of OPAL Balance and its sub-study

AE=adverse event. ATDD=average total daily dose. BID=twice daily. N/A=not applicable. *Average dose assignment was based on ATDD of tofacitinib during OPAL Balance: patients who received an ATDD <15 mg/day were assigned to average tofacitinib 5 mg BID; patients who received an ATDD ≥15 mg/day were assigned to average tofacitinib 10 mg BID. †Constant tofacitinib 5 mg BID included all patients who started OPAL Balance on tofacitinib 5 mg BID and stayed on tofacitinib 5 mg BID (as per sponsor's smoothing algorithm) until switching to tofacitinib 10 mg BID or discontinuing the study. Assessments (including exposure and AEs) after dose switch to tofacitinib 10 mg BID were excluded from the analysis. ‡Number of patients discontinuing or completing were not applicable for the constant tofacitinib 5 mg BID group, as the data were truncated per the constant tofacitinib 5 mg BID definition. §The five patients who withdrew due to pregnancy, and three of the five patients who died, were also recorded on the AE case report form as discontinued due to AE.

Figure 2: Mean (SE) change from baseline in (A) ALT, (B) AST, (C) ALC, (D) ANC, and (E) creatine kinase up to month 48 (ie, main LTE study plus sub-study); observed data

The dashed line represents the time between the baseline (month 0) and month 1 or month 3, as baseline refers to the baseline visit of the qualifying study for patients who enrolled within the 14-day window from the last visit of the qualifying study, or the baseline visit of this LTE study for patients who enrolled outside of the 14-day window from the last visit of the qualifying study. N is the number of patients evaluable at each time point. Only evaluable patients at a visit of interest were included in the analysis and missing values were not imputed. Δ=change from baseline. AE=adverse event. ALC=absolute lymphocyte count. ALT=alanine aminotransferase. ANC=absolute neutrophil count. AST=aspartate aminotransferase. ATDD=average total daily dose. BID=twice daily. LTE=long-term extension. SE=standard error. *Average dose assignment was based on ATDD of tofacitinib during OPAL Balance: patients who received an ATDD <15 mg/day were assigned to average tofacitinib 5 mg BID; patients who received an ATDD ≥15 mg/day were assigned to average tofacitinib 10 mg

BID. †Constant tofacitinib 5 mg BID included all patients who started OPAL Balance on tofacitinib 5 mg BID and stayed on tofacitinib 5 mg BID (as per sponsor's smoothing algorithm) until switching to tofacitinib 10 mg BID or discontinuing the study. Assessments (including exposure and AEs) after dose switch to tofacitinib 10 mg BID were excluded from the analysis.

***Figure 3*: Proportion (SE) of patients reporting (A) ACR20, (B) ACR50, (C) ACR70, (D) PsARC, and (E) PASI75* response, up to month 36 (ie, main LTE study); observed data**

The dashed line represents the time between the baseline (month 0) and month 1, as baseline refers to the baseline of the qualifying study for all patients regardless of their enrolment gaps between the qualifying studies and this study. Only evaluable patients at a visit of interest were included in the analysis and missing values were not imputed. ACR20/50/70=American College of Rheumatology ≥20/50/70% response criteria. ATDD=average total daily dose. BID=twice daily. LTE=long-term extension. PASI=Psoriasis Area and Severity Index. PASI75=≥75% improvement in PASI. PsARC=Psoriatic Arthritis Response Criteria. SE=standard error. *Among patients with plaque psoriasis affecting body surface area ≥3% and PASI >0 at baseline. †Average dose assignment was based on ATDD of tofacitinib during OPAL Balance: patients who received an ATDD <15 mg/day were assigned to average tofacitinib 5 mg BID; patients who received an ATDD ≥15 mg/day were assigned to average tofacitinib 10 mg BID. ‡Constant tofacitinib 5 mg BID included all patients who started OPAL Balance on tofacitinib 5 mg BID and stayed on tofacitinib 5 mg BID (as per sponsor's smoothing algorithm) until switching to tofacitinib 10 mg BID or discontinuing the study. Efficacy assessments after dose switch to tofacitinib 10 mg BID were excluded from the analysis.