Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, up to 36 months in patients with active psoriatic arthritis: data from the second interim analysis of OPAL Balance, an open-label, long-term extension study

P Nash,[1] LC Coates,[2] AJ Kivitz,[3] PJ Mease,[4] DD Gladman,[5] JA Covarrubias-Cobos,[6] D Fleishaker,[7] C Wang,[7] E Kudlacz,[7] S Menon,[7] T Hendrikx,[8] KS Kanik[7]

[1]Department of Medicine, University of Queensland, St Lucia, Brisbane, Australia; [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK; [3]Department of Rheumatology, Altoona Center for Clinical Research, Duncansville, PA, USA; [4]Swedish Medical Center and University of Washington, Seattle, WA, USA; [5]Department of Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada; [6]Unidad Reumatologica Las Americas S.C.P, Mérida, Yucatán, Mexico; [7]Pfizer Inc, Groton, CT, USA; [8]Pfizer Inc, Collegeville, PA, USA

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Introduction

- Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory musculoskeletal disease characterized by joint inflammation, enthesitis, dactylitis, spondylitis, as well as skin and nail lesions. It may lead to joint destruction, progressive disability and reduced quality of life.[1-3]
- Tofacitinib is an oral Janus kinase inhibitor under investigation for the treatment of PsA.
- The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) have been demonstrated in two Phase 3 randomized controlled trials of up to 12 months' duration in patients with active PsA (OPAL Broaden [NCT01877668]; OPAL Beyond [NCT01882439]).[4,5]
- We report interim data up to January 25, 2017 (database not locked; data may change) on the efficacy and safety of tofacitinib in patients with PsA in an ongoing open-label long-term extension (LTE) study (OPAL Balance; NCT01976364).

Objective

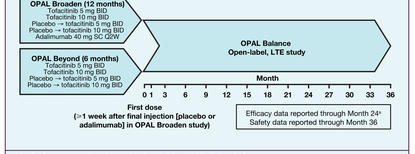
- To evaluate the long-term safety, tolerability (primary objectives), and efficacy (secondary objective) of tofacitinib in adult patients with active PsA in the OPAL Balance study.

Methods

Study design and patients

- Adult patients diagnosed with PsA who met the CIASsification criteria for Psoriatic ARthritis (CASPAR)[6] and had active arthritis and plaque psoriasis at screening were eligible to enter the tofacitinib PsA clinical development program.
- Patients from OPAL Broaden and OPAL Beyond were eligible to enter the OPAL Balance 3-year LTE study ≤3 months after completing or discontinuing the qualifying study for non study-drug-related reasons:
  - Patients in the OPAL Broaden trial had an inadequate response to ≥1 conventional synthetic disease-modifying antirheumatic drug (csDMARD), while OPAL Beyond patients had an inadequate response to tumor necrosis factor inhibitor treatment.
- Upon entry into the LTE study, patients were to receive tofacitinib 5 mg BID for 1 month (Figure 1):
  - After 1 month, doses could be increased to 10 mg BID for efficacy reasons at the investigator's discretion
  - Doses could be reduced back to 5 mg BID for safety reasons at the investigator's discretion.
- Concomitant csDMARD treatment according to local standard-of-care, concomitant oral corticosteroids at a stable dose up to 10 mg prednisone daily (or equivalent) or stable doses of non-steroidal anti-inflammatory drugs, or cyclo-oxygenase 2 inhibitors were allowed but not required.

Figure 1. Study design



[a]Sample sizes were too small beyond this point for meaningful analysis
BID, twice daily; LTE, long-term extension; Q2W, every other week; SC, subcutaneous

Safety and efficacy analyses

- Safety data are reported to Month 36.
- Efficacy data are reported to Month 24 as sample sizes were too small beyond this point for meaningful analysis.
- Reported endpoints:
  - American College of Rheumatology (ACR)20, ACR50, and ACR70 response rates
  - Psoriasis Area and Severity Index 75% improvement (PASI75)
  - Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI; scores range from 0–3, with higher scores indicating greater disability)
  - Change from baseline in Leeds Enthesitis Index (LEI; scores range from 0–6, with higher scores indicating more affected sites)
  - Change from baseline in Dactylitis Severity Score (DSS; scores range from 0–60, with higher scores indicating greater severity)
  - Change from baseline in Patient's Assessment of Arthritis Pain (measured using a visual analog scale of 0 to 100 mm, with higher scores indicating greater arthritis pain).
- Safety and efficacy data from all patients were pooled, regardless of dose, due to flexible dosing between 5 mg and 10 mg BID.

Results

Patients

- All of the 686 patients who enrolled in the LTE study were treated:
  - Of the 422 patients treated in OPAL Broaden, 363 patients enrolled in OPAL Balance
  - Of the 394 patients treated in OPAL Beyond, 323 patients enrolled in OPAL Balance.
- At the data cut-off, 530 (77.3%) patients remained in the study, 154 (22.4%) patients had discontinued and 2 (0.3%) patients had completed the study.
- Mean (range) duration of tofacitinib exposure in the LTE study was 448 (1–1,015) days.
- Patient demographics and baseline disease characteristics represent those at the start of the qualifying study (OPAL Broaden or OPAL Beyond) and are shown in Table 1:
  - Mean duration of PsA was 7.6 years
  - The majority of patients (676 [98.5%]) were receiving concomitant csDMARDs on Day 1; 56 (8.3%) later discontinued and did not restart csDMARD treatment.

Table 1. Patient demographics and baseline disease characteristics

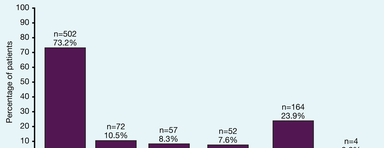
	Tofacitinib treatment (all patients) (N=686)
Patient demographics	
Age, years, mean (SD)	48.8 (11.8)
Female, n (%)	370 (53.9)
White, n (%)	646 (94.2)
BMI, kg/m², mean (SD)	29.6 (6.1)
Baseline disease characteristics	
Duration of PsA, years, mean (SD)	7.6 (7.2)
Plaque psoriasis affecting BSA ≥3%, n (%)	475 (69.2)
PASI score,[a] median (range) [N1]	7.3 (0.3–66.0) [474]
HAQ-DI score, mean (SD)	1.2 (0.7)
LEI,[b] mean (SD)	2.8 (1.6)
DSS,[b] mean (SD)	8.4 (8.2)
Concomitant oral corticosteroid use on Day 1, n (%)	133 (19.4)
Concomitant csDMARD use on Day 1, n (%)	
Methotrexate	548 (79.9)
Other[c]	128 (18.7)

[a]Among patients with plaque psoriasis affecting BSA ≥3% and PASI >0 at baseline; [b]Among patients with baseline score >0; [c]Includes sulfasalazine, leflunomide, hydroxychloroquine, and chloroquine
BMI, body mass index; BSA, body surface area; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DSS, Dactylitis Severity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; LEI, Leeds Enthesitis Index; N1, number of patients with plaque psoriasis affecting BSA ≥3% and PASI >0 at baseline; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation

Safety

- By Month 36, 1,685 adverse events (AEs) had been reported in 502 (73.2%) patients (Figure 2):
  - Seventy-two (10.5%) patients had experienced serious AEs (SAEs)
  - Fifty-two (7.6%) patients discontinued due to AEs.

Figure 2. Safety assessment up to Month 36 in the LTE study



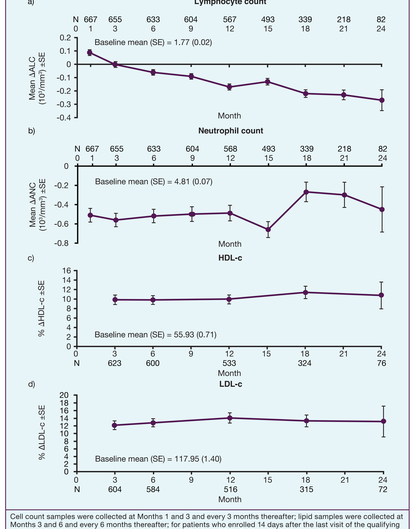
[a]An AE that interferes significantly with a patient's usual function; [b]Permitted dose reduction: tofacitinib doses previously increased to 10 mg BID could be reduced back down to 5 mg BID at the investigator's discretion for safety reasons; Number of patients in safety analysis set, N=686
AE, adverse event; BID, twice daily; LTE, long-term extension; SAE, serious adverse event

- By Month 36, four (0.6%) patients had died in the LTE study due to pancreatic adenocarcinoma, acute cardiac failure secondary to hypertensive heart disease, chronic obstructive pulmonary disease, and pulmonary embolism. These deaths were not related to the study treatment per the Investigator's opinion.
- The most common AEs were upper respiratory tract infection (11.4%), nasopharyngitis (10.6%), and urinary tract infection (6.4%).
- AEs of special interest were reported through Month 36:
  - Eleven patients (1.6%) reported serious infection events
  - There were 19 (2.8%) cases of herpes zoster reported, of which a case of facial herpes zoster was an SAE
    - There were 17 cases of single dermatome herpes zoster and two cases of multidermatomal herpes zoster
    - The two cases of multidermatomal herpes zoster were adjudicated as opportunistic infections; no non-herpes zoster, non-tuberculosis (TB) opportunistic infections were reported
  - Four AEs of latent TB were reported in patients whose previously negative QuantiFERON response became positive; however, no cases of active TB were reported
  - Two (0.3%) patients reported major adverse cardiovascular events
    - One case of sudden cardiac failure resulted in death
    - One patient experienced a non-fatal myocardial infarction
  - Thirteen (1.9%) patients reported malignancies, including one fatal case of pancreatic adenocarcinoma, which was reported after 85 days on tofacitinib in the OPAL Balance study (after 12 months of therapy with adalimumab in the OPAL Broaden qualifying study)
  - No cases of gastrointestinal perforation or inflammatory bowel disease were reported
  - One case of uveitis was reported.

Laboratory parameters

- Few patients experienced elevated liver enzyme levels:
  - Alanine aminotransferase (ALT) was elevated ≥3 times the upper limit of normal (ULN) in 20 (2.9%) patients
  - Aspartate aminotransferase (AST) was elevated ≥3 times the ULN in 11 (1.6%) patients.
- Four (0.6%) patients met discontinuation criteria for laboratory values:
  - One patient discontinued due to two sequential increases of hemoglobin values of <8.0 g/dL or decreases of >30% from baseline value
  - One patient discontinued due to two sequential platelet counts <75x10⁹/L
  - One patient discontinued due to two sequential AST or ALT elevations ≥5 times the ULN regardless of total bilirubin or accompanying signs or symptoms
  - One patient discontinued due to two sequential increases in serum creatinine >50% and an increase >0.5 mg/dL over the average of screening and baseline.
- No other patients had laboratory parameters that met criteria for discontinuation (neutrophil count, hemoglobin, lymphocyte count, platelet count, or creatine kinase).
- There was a modest mean percentage increase from baseline in the qualifying studies which was maintained in the LTE in total cholesterol and triglycerides (not shown), low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol (Figure 3).
- Twenty-seven (3.9%) patients started new lipid-lowering medication during the LTE (82 [12.0%] patients were on lipid-lowering drugs at baseline).

Figure 3. Change in laboratory parameters over time

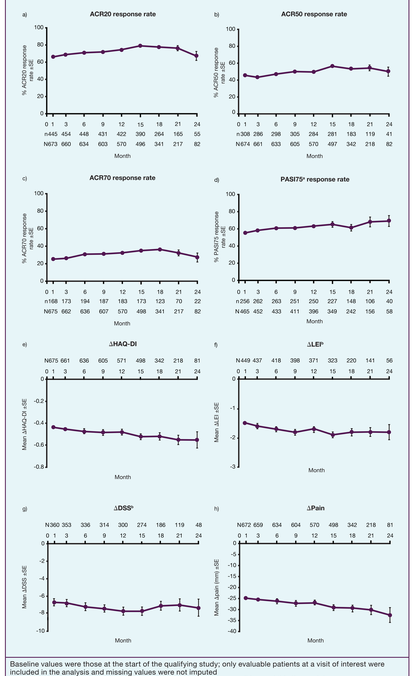


Cell count samples were collected at Months 1 and 3 and every 3 months thereafter; lipid samples were collected at Months 3 and 6 and every 6 months thereafter; for patients who enrolled 14 days after the last visit of the qualifying study, the baseline values come from the baseline visit of the OPAL Balance study; otherwise the baseline values come from the qualifying studies
Δ, change from qualifying study baseline; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; N, number of patients at each time point; SE, standard error

Efficacy

- The efficacy of tofacitinib was maintained over time in the LTE.
- At Month 24, 55/82 (67.1%), 41/82 (50.0%), and 22/82 (26.8%) patients had an ACR20, ACR50, and ACR70 response, respectively (Figure 4a–c), and 40/58 (69.0%) patients achieved PASI75 (Figure 4d).
- Reductions from baseline in HAQ-DI, LEI, DSS, and pain were maintained throughout the LTE study to Month 24 (Figure 4e–h).

Figure 4. Efficacy data up to Month 24



Baseline values were those at the start of the qualifying study; only evaluable patients at a visit of interest were included in the analysis and missing values were not imputed
Efficacy data are reported to Month 24 as sample sizes were too small beyond this time point
[a]Among patients with plaque psoriasis affecting BSA ≥3% and PASI >0 at qualifying study baseline;
[b]Among patients with baseline score >0
ACR20, American College of Rheumatology 20% response rate; ACR50, American College of Rheumatology 50% response rate; ACR70, American College of Rheumatology 70% response rate; BSA, body surface area; DSS, Dactylitis Severity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; LEI, Leeds Enthesitis Index; N, number of patients at each time point; n, number of patients with response; PASI, Psoriasis Area and Severity Index; PASI75, PASI 75% improvement; SE, standard error

Conclusions

- **In this second interim analysis of data from patients with active PsA receiving tofacitinib for up to 36 months in the LTE study, OPAL Balance:**
  - **The safety profile of tofacitinib was generally similar to that reported in the OPAL Broaden and OPAL Beyond qualifying PsA studies[4,5]**
  - **Overall rates of laboratory changes were generally consistent with those observed in the OPAL Broaden and OPAL Beyond qualifying PsA studies; incidences of meaningful changes from baseline were modest and appeared relatively stable over time**
  - **No new safety signals were identified compared with the known safety profile of tofacitinib in other patient populations**
  - **The efficacy of tofacitinib across various PsA disease domains was maintained over time in the LTE.**

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Disclosure of interest

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