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

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Abstract

Introduction Tofacitinib is an oral Janus kinase inhibitor for the treatment of psoriatic arthritis (PsA).

Objective Our objective was to compare the incidence rates (IRs) of adverse events in tofacitinib clinical trials and real-world observational data for alternative treatments.

Methods The tofacitinib “dose-comparison cohort” included months 0–12 of two phase III studies (tofacitinib 5 [n = 238] and 10 [n = 236] mg twice daily [BID]); the “all-tofacitinib comparison cohort” (n = 783) included two phase III and one ongoing long-term extension study (data cutoff May 2016). An “observational comparison cohort” (n = 5799) comprised patients initiating a conventional synthetic disease-modifying antirheumatic drug (DMARD), biologic DMARD, or apremilast in the US Truven MarketScan database from 2010 to 2015. IRs for serious infections (SIEs; requiring hospitalization), herpes zoster (HZ), malignancies (excluding non-melanoma skin cancer [NMSC]), NMSC, and major adverse cardiovascular events (MACE) across cohorts were qualitatively compared.

Results IRs (patients with events/100 patient-years) for SIEs were similar between the tofacitinib dose-comparison cohort (5 mg BID: 1.3; 10 mg BID: 2.0) and the observational comparison cohort (1.1–7.9; treatment dependent). The tofacitinib dose-comparison cohort had a higher rate of HZ (5 mg BID: 2.0; 10 mg BID: 2.7) than did the observational comparison cohort (0.8–2.0). IRs for NMSC were generally lower in the all-tofacitinib comparison cohort (0.5) than in the observational comparison cohort (0.4–6.0). IRs for MACE, malignancies excluding NMSC, and NMSC were similar between cohorts.

Conclusion In patients with PsA, tofacitinib had a safety profile similar to that of other systemic therapies in real-world settings, except for the risk of HZ, a known risk of tofacitinib.

Trial Registration ClinicalTrials.gov: NCT01877668; NCT01882439; NCT01976364.

Key Points

In patients with active psoriatic arthritis (PsA), the safety profile of tofacitinib was generally consistent with that of other therapies in real-world settings.

Tofacitinib was associated with a higher risk for herpes zoster than were most other PsA therapies.

No new risks were identified compared with those already observed with tofacitinib treatment of rheumatoid arthritis.
1 Introduction

Psoriatic arthritis (PsA) is an immune-mediated systemic inflammatory disease with multiple disease manifestations, including peripheral arthritis, enthesitis, dactylitis, spondylitis, and skin and nail psoriasis [1]. Treatment recommendations for patients with PsA from the European League Against Rheumatism [2] and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis [1] vary according to adverse prognostic risk factors, disease manifestations, and responsiveness to prior treatment. Current approved treatments for PsA include nonsteroidal anti-inflammatory drugs, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and the targeted synthetic DMARD (tsDMARD) apremilast [1–3]. There are safety concerns with most established therapies for PsA [4], including gastrointestinal adverse events (AEs), hepatotoxicity, opportunistic infections (OIs) including tuberculosis, serious infections (SIEs), malignancy, and—in rare instances—bone marrow toxicity [5–9].

Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. We describe the safety profile of tofacitinib in PsA, using pooled data from two phase III [10, 11] and one ongoing long-term extension (LTE) study [12], and compare the incidence rates (IRs) for AEs of special interest from the ongoing long-term extension (LTE) study [12], and compare the incidence rates (IRs) for AEs of special interest from the tofacitinib PsA clinical program with those from observational data from all patients who received one or more dose of tofacitinib in the phase III or LTE studies (including patients who advanced to tofacitinib 5 mg BID for safety reasons at any time).

2 Methods

2.1 Study Design

Safety data for patients in two global phase III studies (OPAL Broaden [NCT01877668] [10] and OPAL Beyond [NCT01882439] [11]) and one LTE study (OPAL Balance [NCT01976364] [12]) were pooled for analysis. OPAL Broaden and OPAL Beyond, studies of 12- or 6-months duration, respectively, have been described previously [11, 12]. Briefly, both were double-blind, placebo-controlled, parallel-group studies in patients with active PsA. Patients in OPAL Broaden were tumor necrosis factor inhibitor (TNFi) naïve and had an inadequate prior response to one or more csDMARD. Patients in OPAL Beyond had an inadequate response to one or more prior TNFi. In both studies, patients were randomized to receive tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, placebo advancing to tofacitinib 5 mg BID after 3 months, or placebo advancing to tofacitinib 10 mg BID after 3 months. In both studies, patients received one background csDMARD. In OPAL Broaden, patients were also randomized to receive adalimumab 40 mg subcutaneously every 2 weeks (Q2W).

OPAL Balance [12] is an ongoing, open-label LTE study (database not locked) that enrolled patients who had participated in OPAL Broaden or OPAL Beyond. Data up to 10 May 2016 were included in the current analysis, including up to 3 years of tofacitinib exposure per patient. Upon entry, all patients received tofacitinib 5 mg BID. Tofacitinib dose could be increased to 10 mg BID at the investigator’s discretion after 1 month and could be decreased from 10 mg BID to 5 mg BID for safety reasons at any time.

2.2 Tofacitinib Clinical Trial Cohorts

Three analysis cohorts were defined (Fig. 1): (1) the tofacitinib “placebo-controlled cohort” comprised data from the placebo-controlled portion (months 0–3) of the phase III studies (all treatment groups); (2) the “tofacitinib dose-comparison cohort” included the same tofacitinib-treated patients at baseline as in the placebo-controlled cohort but included the entire length of both studies in patients randomized to tofacitinib 5 or 10 mg BID (OPAL Broaden, months 0–12; OPAL Beyond, months 0–6); and (3) the “all-tofacitinib comparison cohort” comprised data from all patients who received one or more dose of tofacitinib in the phase III or LTE studies (including patients in the placebo-controlled and dose-comparison cohorts and patients who advanced from placebo to tofacitinib after their first dose of tofacitinib). Baseline demographics and characteristics were shared for cohorts 1 and 2 and were separate for cohort 3.

2.3 Observational Comparison Cohort

The “observational comparison cohort” included real-world data from adult patients receiving approved PsA therapies in the US Truven MarketScan database, comprising data from privately and publicly insured US patients obtained from employers and health plans. Patients had a diagnosis of PsA, defined by either one or more inpatient, or two or more outpatients (provided on two unique calendar days, 1 January 2010–30 September 2015) International Classification of Disease (ICD) diagnosis codes of 696.0 (psoriatic arthropathy); at least one code had to be assigned by a rheumatologist. Patients must have been aged ≥18 years, have initiated therapy with a systemic agent for PsA (csDMARD, bDMARD, or tsDMARD; as a proxy definition for active moderate to severe disease), and have been enrolled in the database for ≥12 months before the index date (date of first prescription or administration for PsA treatment, or first procedure date following confirmation of PsA diagnosis for infusion therapies), with no data gap >30 days. Patient exclusion criteria reflecting those of
the phase III tofacitinib studies were applied where possible (see Online Resource 1). Patients receiving tofacitinib were not included in the observational cohort because tofacitinib was not yet approved at the time of the analysis.

Patients were classified by initiation of approved PsA therapies, in nonmutually exclusive categories: (1) bDMARD (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, secukinumab); (2) bDMARD + csDMARD (methotrexate, leflunomide, sulfasalazine); (3) TNFi (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol); (4) TNFi + csDMARD; and (5) individual therapies (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, apremilast).

2.4 Outcomes and Analyses

2.4.1 Tofacitinib Clinical Trial Cohorts

Events analyzed included AEs, deaths, serious AEs (SAEs), and AEs leading to discontinuation. AEs of special interest were SIEs (infections requiring parenteral antimicrobials in an emergency department setting or infections resulting in hospitalization or prolonging an existing hospitalization), herpes zoster (HZ), OIs (excluding tuberculosis) [13], tuberculosis, major adverse cardiovascular events (MACE), malignancies (excluding non-melanoma skin cancer [NMSC]), and NMSC. Adjudication of AEs is detailed in Online Resource 1.

Common AEs (occurring in ≥ 2% of patients in any group) were analyzed in the placebo-controlled tofacitinib cohort, including data up to 3 months. SAEs, discontinuations due to AEs, and infections were analyzed in the tofacitinib dose-comparison cohort, including data up to 12 months. MACE, malignancies (excluding non-melanoma skin cancer [NMSC]), and NMSC were evaluated in the all-tofacitinib comparison cohort because of the lower frequency of these events and the longer latency of MACE, malignancies (excluding NMSC), and NMSC. Tofacitinib exposure in patient-years was calculated based on the total follow-up time to the day of the first event within the event-counting period for patients with events or until 28 days after the last study drug dose (or to the end of the study) for patients without events. IRs were defined as the
number of patients with one or more events/100 patient-years of treatment exposure along with 95% confidence intervals (CIs) [14]; IRs and the number of patients with an AE included AEs occurring up to 28 days beyond the last dose of study treatment (or to the data cutoff date for OPAL Balance). A 28-day risk period was applied to prevent inflated IR estimations due to potential differences between elapsed time and exposure time. Analyses were descriptive, with no formal statistical testing of differences between groups.

### 2.4.2 Observational Comparison Cohort

Outcomes in the observational comparison cohort were defined via ICD-9 codes, with algorithms validated in medical claims databases [13, 15–30], and included all incident events occurring from the index date until the time of first occurrence of AEs of each type, the earliest date of death, loss of medical or pharmacy coverage, date of switch to another bDMARD or apremilast, discontinuation of the specific PsA treatment, or the end of the study (30 September 2015). Outcomes were weighted by previous TNFi use, concomitant methotrexate use, and concomitant steroid use to control for observed differences in patient population characteristics between the tofacitinib global clinical studies and the observational comparison cohort (further details in Online Resource 1).

As several PsA therapies and combinations of therapies were studied, patients were permitted to contribute person–time data to one or more exposure category if they switched PsA treatments. IRs reflected the time to first event of each type, e.g., if a patient initiated etanercept and experienced an SIE (defined as infections occurring during hospitalization; see Online Resource 1) and then subsequently initiated adalimumab and experienced another SIE, both exposures and infection events were deemed to have contributed to the respective IRs for etanercept and adalimumab and to the composite exposure categories for TNFi and bDMARDs.

IRs were calculated for SIEs, OIs, HZ, malignancies (excluding NMSC), NMSC, and MACE from the observational comparison cohort. IRs were calculated for events occurring during treatment or up to predefined intervals beyond the estimated last dose of PsA treatment, which considered the variable latency period for developing each type of AE: 30 days for SIEs and HZ, 90 days for MACE, and all available follow-up time for malignancies.

### 3 Results

#### 3.1 Patients

##### 3.1.1 Placebo-Controlled and Tofacitinib Dose-Comparison Cohorts

A total of 474 tofacitinib-treated, 106 adalimumab-treated, and 236 placebo-treated patients were included in the placebo-controlled cohort (Table 1). The tofacitinib dose-comparison cohort included the same 474 tofacitinib-treated patients as the placebo-controlled cohort (Table 1). Patient demographics were generally similar across tofacitinib and placebo groups (Table 1). The adalimumab group included a smaller proportion of patients from the USA and Canada and a larger proportion from Eastern Europe and Russia than the other groups and also had a shorter duration of PsA. This reflected the fact that all patients treated with adalimumab were from OPAL Broaden only, which had a different geographical spread from that in OPAL Beyond and required patients to be TNFi naïve.

The lowest proportion of patients taking corticosteroids at baseline was in the tofacitinib 10 mg BID group (15.7%), and the highest proportion was in the tofacitinib 5 mg BID group (28.2%). All patients were receiving one background csDMARD, with most patients receiving methotrexate (75.5–81.8%).

##### 3.1.2 All-Tofacitinib Comparison Cohort

The all-tofacitinib comparison cohort included 783 tofacitinib-treated patients, with a total of 776 patient-years of tofacitinib exposure (all doses). Table 2 presents demographic data and baseline characteristics for the all-tofacitinib comparison cohort.

##### 3.1.3 Observational Comparison Cohort

A total of 5799 patients meeting the selection criteria were identified in the US Truven MarketScan database. All patients were from the USA, with mean age, sex, and diabetes history comparable to those of the all-tofacitinib comparison cohort (Table 2). However, more patients in the all-tofacitinib comparison cohort had prior experience with TNFi and methotrexate and were taking corticosteroids at baseline than in the observational comparison cohort.
3.2  Outcomes

3.2.1  Overview of Adverse Events

In the placebo-controlled tofacitinib cohort, headache (tofacitinib 5 mg BID: 3.8%; 10 mg BID: 8.5%), nasopharyngitis (tofacitinib 5 mg BID: 5.9%; 10 mg BID: 5.5%), and upper respiratory tract infection (tofacitinib 5 mg BID: 5.0%; 10 mg BID: 4.7%) were the most commonly reported AEs in patients receiving tofacitinib over 3 months (see the table in Online Resource 1). IRs for SAEs over 12 months for tofacitinib 5 and 10 mg BID in the tofacitinib dose-comparison cohort were 7.9 (95% CI 4.1–13.8) and 8.1 (95% CI 4.2–14.2), respectively. Discontinuations due to AEs occurred in 11 patients randomized to each of tofacitinib 5 and 10 mg BID, with IRs of 7.2 (95% CI 3.6–12.8) and 7.3 (95% CI 3.7–13.1), respectively (a further three discontinuations occurred in the tofacitinib 10 mg BID group because of AEs reported outside the 28-day risk period).

3.2.2  Serious Infections

In the tofacitinib dose-comparison cohort (12 months), SIEs (infections requiring parenteral antimicrobials in an outpatient or emergency department setting or resulting in hospitalization) were experienced by two patients receiving tofacitinib 5 mg BID (IR 1.3; 95% CI 0.2–4.7) and three receiving tofacitinib 10 mg BID (IR 2.0; 95% CI 0.4–5.8) (Fig. 2a). Of these, only pneumonia occurred in one or more patient (n = 2) and was resolved with conventional therapy. All SIEs in the tofacitinib dose-comparison cohort were the result of hospitalization; no outpatient infections requiring parenteral antibiotics were reported. Across all tofacitinib-treated patients in the phase III and LTE studies (the all-tofacitinib comparison cohort), SIEs occurred in 11 patients during treatment or within 28 days of the last dose of tofacitinib (IR 1.4; 95% CI 0.7–2.5); SIEs were reported in two additional patients > 28 days after their last dose of tofacitinib.

For patients in the observational comparison cohort, the IR for SIEs (defined as infections resulting in hospitalization) was 2.2 (95% CI 1.4–3.2) for bDMARDs, ranging from 1.1 (95% CI 0.5–2.2) to 7.9 (95% CI 0.8–30.0)

| Characteristics                  | Tofacitinib 5 mg BID (n = 238) | Tofacitinib 10 mg BID (n = 236) | Placebo (n = 236) | Adalimumab 40 mg Q2Wa (n = 106) |
|----------------------------------|---------------------------------|---------------------------------|------------------|---------------------------------|
| Age (years)                      | 49.5 ± 12.4                     | 49.4 ± 11.7                     | 48.4 ± 12.5      | 47.4 ± 11.3                     |
| Female                           | 121 (51)                        | 136 (58)                        | 136 (58)         | 50 (47)                         |
| BMI (kg/m²)                      | 29.8 ± 6.3                      | 30.2 ± 6.3                      | 29.2 ± 5.6       | 28.8 ± 5.3                      |
| Race                             |                                 |                                 |                  |                                 |
| White                            | 226 (95.0)                      | 221 (93.6)                      | 222 (94.1)       | 103 (97.2)                      |
| Black                            | 1 (0.4)                         | 1 (0.4)                         | 1 (0.4)          | 0 (0.0)                         |
| Asian                            | 2 (0.8)                         | 10 (4.2)                        | 9 (3.8)          | 2 (1.9)                         |
| Other                            | 9 (3.8)                         | 4 (1.7)                         | 4 (1.7)          | 1 (0.9)                         |
| Geographical regionb             |                                 |                                 |                  |                                 |
| USA/Canada                       | 58 (24.4)                       | 56 (23.7)                       | 45 (19.1)        | 11 (10.4)                       |
| Eastern Europe/Russia            | 93 (39.1)                       | 100 (42.4)                      | 112 (47.5)       | 72 (67.9)                       |
| Western Europe/Australia         | 58 (24.4)                       | 59 (25.0)                       | 49 (20.8)        | 17 (16.0)                       |
| Asia                             | 1 (0.4)                         | 7 (3.0)                         | 6 (2.5)          | 1 (0.9)                         |
| Latin America                    | 28 (11.8)                       | 14 (5.9)                        | 24 (10.2)        | 5 (4.7)                         |
| PsA duration (years)             | 8.6 ± 7.9                       | 7.5 ± 6.6                       | 8.1 ± 7.5        | 5.3 ± 5.3                       |
| Corticosteroid usec             | 67 (28.2)                       | 37 (15.7)                       | 49 (20.8)        | 23 (21.7)                       |
| Concomitant MTX                   | 190 (79.8)                      | 184 (78.0)                      | 193 (81.8)       | 80 (75.5)                       |

Data are presented as mean ± standard deviation or N (%) unless otherwise indicated
BID twice daily, BMI body mass index, MTX methotrexate, PsA psoriatic arthritis, Q2W once every 2 weeks
aPatients from OPAL Broaden receiving adalimumab 40 mg Q2W subcutaneously
bEastern Europe includes Bulgaria, Czech Republic, Hungary, Poland, and Slovakia. Western Europe includes Belgium, France, Germany, Spain, and the UK. Asia includes Taiwan. Latin America includes Brazil and Mexico
cOral systemic corticosteroid use at baseline (maximum dose 10 mg/day prednisone equivalent)
across all treatments (Fig. 2a). When considering SIEs defined as infection events requiring parenteral antimicrobial treatment in an emergency department setting or resulting in hospitalization, similar IRs for SIEs were reported for the observational comparison cohort (ranging from 1.3 [95% CI 0.6–2.5] to 8.1 [95% CI 0.9–29.9]) (Fig. 2b) as the tofacitinib dose-comparison cohort.

### 3.2.3 Herpes Zoster

In the tofacitinib dose-comparison cohort, HZ events were reported for three patients receiving tofacitinib 5 mg BID (IR 2.0; 95% CI 0.4–5.7) and four receiving tofacitinib 10 mg BID (IR 2.7; 95% CI 0.7–6.8) (Fig. 3a). HZ events were reported in 16 patients receiving tofacitinib in the all-tofacitinib cohort (IR 2.1; 95% CI 1.2–3.3). For patients in the observational comparison cohort, IRs for HZ ranged from 0.8 (95% CI 0.3–1.5) to 2.0 (95% CI 0.8–4.0) across treatments, with the IR for infliximab (2.0; 95% CI 0.8–4.0) being most similar to that reported for tofacitinib 5 mg BID in the tofacitinib dose-comparison cohort (Fig. 3a).

### 3.2.4 Opportunistic Infections

In total, three adjudicated OIs occurred in the all-tofacitinib comparison cohort (two patients receiving tofacitinib 5 mg BID and one receiving tofacitinib 10 mg BID; IR 0.4; 95% CI 0.1–1.1) (Fig. 3b). All were cases of multidermatomal HZ and were resolved. A case of HZ with two adjacent dermatomes in a patient receiving tofacitinib 5 mg BID was not included in the IR calculation for OI, as it was classified as a special interest infection. No cases of active tuberculosis were reported in tofacitinib-treated patients. For patients in the observational comparison cohort, IRs for OI ranged from 0.9 (95% CI 0.4–1.7) to 3.8 (95% CI 0.7–11.6) across treatments (Fig. 3b).

### 3.2.5 Major Adverse Cardiovascular Events

MACE were reported in three patients in the all-tofacitinib comparison cohort (IR 0.4; 95% CI 0.1–1.1) (Fig. 4a) and included sudden cardiac death (after advancing from placebo to tofacitinib 5 mg BID for 57 days), myocardial infarction (after receiving tofacitinib 5 mg BID for 197 days), and ischemic stroke (after receiving tofacitinib 10 mg BID for 80 days). For patients in the observational comparison cohort, IRs for MACE ranged from 0.0 (95% CI 0.0–1.6) to 0.7 (95% CI 0.1–2.4) across treatments (Fig. 4a).

### 3.2.6 Malignancies

Malignancies (excluding NMSC) were reported in five patients in the all-tofacitinib comparison cohort (IR 0.6; 95% CI 0.2–1.5) (Fig. 4b). These were bladder transitional cell carcinoma (after receiving tofacitinib 5 mg BID for 48 days); renal cell carcinoma (after receiving adalimumab 40 mg Q2W for 342 days followed by tofacitinib 5 mg BID for 32 days); metastatic pancreatic cell carcinoma (after receiving adalimumab 40 mg Q2W for 353 days followed by tofacitinib 5 mg BID for 84 days); renal cell carcinoma of the vulva (after receiving tofacitinib 5 mg BID for 65 days); and invasive ductal breast carcinoma (after receiving tofacitinib 5 mg BID for 244 days). For patients in the observational comparison cohort, IRs for malignancies (excluding NMSC) ranged from 0.0 (95% CI 0.0–1.6) to 1.1 (95% CI 0.3–2.8) across treatments (Fig. 4b).

### 3.2.7 Malignancies

Malignancies (excluding NMSC) were reported in five patients in the all-tofacitinib comparison cohort (IR 0.6; 95% CI 0.2–1.5) (Fig. 4b). These were bladder transitional cell carcinoma (after receiving tofacitinib 5 mg BID for 48 days); renal cell carcinoma (after receiving adalimumab 40 mg Q2W for 342 days followed by tofacitinib 5 mg BID for 32 days); metastatic pancreatic cell carcinoma (after receiving adalimumab 40 mg Q2W for 353 days followed by tofacitinib 5 mg BID for 84 days); renal cell carcinoma of the vulva (after receiving tofacitinib 5 mg BID for 65 days); and invasive ductal breast carcinoma (after receiving tofacitinib 5 mg BID for 244 days). For patients in the observational comparison cohort, IRs for malignancies (excluding NMSC) ranged from 0.0 (95% CI 0.0–1.6) to 1.1 (95% CI 0.3–2.8) across treatments (Fig. 4b). NMSC was reported in four patients in the all-tofacitinib comparison cohort (IR 0.5; 95% CI 0.1–1.3) and included two basal cell and two squamous cell carcinomas. All NMSC were reported in White patients: two from Australia...
and one each from Belgium and the USA. For patients in the observational comparison cohort, IRs for NMSC ranged from 0.4 (95% CI 0.1–1.1) to 6.0 (95% CI 1.7–14.9) across treatments (Fig. 4c).

### 3.2.7 Deaths

Four deaths occurred in the tofacitinib PsA clinical program. Two occurred in the all-tofacitinib comparison cohort during treatment or within 28 days of the last tofacitinib
The tofacitinib dose-comparison cohort included patients who were randomized to receive either tofacitinib 5 mg BID or 10 mg BID (n=474) in the two phase III studies (12 or 6 months’ duration). OI included HZ and excluded tuberculosis. Observational comparison cohort outcomes were weighted based on previous TNFi use (identified using all available data: TNFi naïve vs. TNFi experienced), concomitant MTX use (identified using data from the index date to 90 days before the index date: MTX only vs. no MTX or with other csDMARDs), and concomitant steroid use (identified on the index date: steroid use vs. no steroid use); the weights were derived using the all-tofacitinib comparison cohort data. For bDMARD, bDMARD + csDMARD, TNFi, and TNFi + csDMARD, n refers to “treatment episodes” rather than patients, as the patients in these groups may have initiated more than one drug in the given class. bDMARD biologic DMARD, BID twice daily, CI confidence interval, csDMARD conventional synthetic DMARD, DMARD disease-modifying antirheumatic drug, HZ herpes zoster, IR incidence rate (patients with event/100 PY), MTX methotrexate, OI opportunistic infection, PY patient-years, TNFi tumor necrosis factor inhibitor, tofa tofacitinib

3.2.8 Clinical Laboratory Findings

Overall, clinical laboratory findings were in line with those observed in other clinical programs for tofacitinib (see Online Resource 1).

4 Discussion

This post hoc analysis of data from two phase III studies and one LTE study examined the safety profile of tofacitinib in patients with active PsA and compared IRs for AEs
Fig. 4  IRs for a MACE, b malignancies (excluding NMSC), and c NMSC across cohorts. The all-tofacitinib comparison cohort included patients who received at least one dose of either tofacitinib 5 mg BID or 10 mg BID (n=783) in either of the two phase III studies or the LTE. Observational comparison cohort outcomes were weighted based on previous TNFi use (identified using all available data: TNFi naïve vs. TNFi experienced), concomitant MTX use (identified using data from the index date to 90 days before the index date: MTX only vs. no MTX or with other csDMARDs), and concomitant steroid use (identified on the index date: steroid use vs. no steroid use); the weights were derived using the all-tofacitinib comparison cohort data. For bDMARD, bDMARD + csDMARD, TNFi, and TNFi + csDMARD, n refers to “treatment episodes” rather than patients, as the patients in these groups may have initiated more than one drug in the given class. bDMARD biologic DMARD, BID twice daily, CI confidence interval, csDMARD conventional synthetic DMARD, DMARD disease-modifying antirheumatic drug, IR incidence rate (patients with event/100 PY), LTE long-term extension, MACE major adverse cardiovascular event, MTX methotrexate, NMSC non-melanoma skin cancer, PY patient-years, TNFi tumor necrosis factor inhibitor, tofa tofacitinib.
of special interest with observational data for other PsA
treatments.

The types and rates of AEs were similar to those observed
with tofacitinib in clinical programs for other indications
[31–33], with nasopharyngitis, headache, and upper
respiratory tract infections the most commonly reported
AEs during the first 3 months of tofacitinib treatment. AEs
in the placebo group may reflect in part the fact that all
patients were receiving background csDMARD treatment.
IRs for SAEs in patients receiving tofacitinib 5 and 10 mg
BID for up to 12 months were 7.9 and 8.1, respectively,
and were similar to the IR of 9.4 reported for all tofacitinib
doses across phase I, II, III, and LTE studies in rheumatoid
arthritis (RA) [31]. IRs for treatment discontinuation due
to AEs in the PsA dose-comparison cohort for patients
receiving tofacitinib 5 and 10 mg BID were 7.2 and 7.3,
respectively, and were also similar to the IR of 7.5 reported
for all tofacitinib doses in patients with RA [31].

Increased rates of SIEs are an acknowledged risk of
medications that have an immunomodulatory effect,
including tofacitinib and bDMARDs [31, 34, 35]. The IRs
for SIEs in the tofacitinib dose-comparison cohort (1.3 and
2.0 for patients with PsA receiving tofacitinib 5 and 10 mg
BID, respectively) and in the all-tofacitinib comparison
cohort (1.4) were consistent with the IR of 2.7 reported
for tofacitinib in patients with RA who participated in phase I,
II, III, and LTE studies [31] and 1.9 in patients with psoriasis
in phase III and LTE studies [32]. The IRs for SIEs with
tofacitinib in patients with PsA were also within the range
of 1.7–4.7 reported for other systemic PsA therapies in the
observational comparison cohort.

Analyses of data from the tofacitinib RA and psoriasis
clinical programs identified increased rates of HZ infec-
tion with tofacitinib versus placebo [36, 37]. In the cur-
cent analysis, the IRs for HZ in patients with PsA were
2.0, 2.7, and 2.1 for patients with PsA receiving tofacitinib
5 and 10 mg BID in the tofacitinib dose-comparison cohort
and those in the all-tofacitinib comparison cohort, respect-
ively. These IRs were somewhat higher than the IRs of 1.1
(95% CI 0.5–2.4) and 2.0 (95% CI 1.1–3.4) reported for
tofacitinib 5 and 10 mg BID, respectively, in two 12-month
studies in patients with chronic plaque psoriasis [32] but
lower than the IR of 3.9 (95% CI 3.6–4.2) reported for
the pooled analysis of data from phase I, II, III, and LTE
studies in the RA clinical program (all tofacitinib doses) [31].
As noted earlier in this section, this may reflect the fact
that tofacitinib was administered as monotherapy in the psoria-
sis studies (i.e., without corticosteroids or other background
immunomodulators) but was more frequently administered
with (56.0%) than without concomitant corticosteroids in the
RA studies [31], which has been shown to increase the risk
of HZ [38]. Although using corticosteroids in combination
with csDMARDs has also been associated with higher rates
of HZ, csDMARDs have not been identified as an independ-
ent risk factor for HZ [38], and their use in the PsA studies
was actually higher than that in the RA studies [31]. OIs are
also considered a risk with tofacitinib [31, 39], as well as
with biologic therapies [13], but in this analysis—other than
three cases of multidermatomal HZ (out of 16 total cases)—
no infections were adjudicated to be OIs. By comparison,
IRs for HZ in the observational comparison cohort were
generally lower, ranging from 0.8 to 2.0.

The IR for malignancies (excluding NMSC) in patients
with PsA in the all-tofacitinib comparison cohort (0.6) was
within the range reported for other PsA treatments in the
observational comparison cohort (0.0–1.1). Of the five
malignancy events, four occurred within the first 3 months
of tofacitinib treatment, and all were different types of
malignancy. The IR for NMSC in patients with PsA in
the all-tofacitinib comparison cohort (0.5) appeared lower
than the range observed in the observational comparison
cohort for other agents (0.8–6.0), except for golimumab
(0.4). However, the higher IRs for NMSC in the observa-
tional comparison cohort may be reflective of clinical trial
populations receiving more intense follow-up, even during
the trial screening process. Although misclassifications of
outcomes in claims data are possible, the approach used here
mirrors that of previous high-quality validation studies that
have demonstrated high positive predictive values compared
with the gold standard or medical record review [13, 15–30].
In addition, differences in incidence of NMSC have been
reported based on geographical region [40] and, while the
tofacitinib clinical studies were conducted at centers world-
wide, the observational data cohort was based on patients
from the USA only. However, the IRs for patients with PsA
in the tofacitinib studies were similar to those reported for
bDMARD exposures in external sources [41–43] and were
consistent with results from pooled analyses of patients
receiving tofacitinib in the RA [31] and psoriasis [32] clin-
cal programs.

Patients with PsA have an increased risk of cardiovascu-
lar morbidity and mortality compared with the general pop-
ulation [44–46]. Modest, dose-dependent changes in lipid
profile were observed in tofacitinib-treated patients with
PsA [10, 11]; however, this did not appear to correlate with
increased cardiovascular risk, and the incidence of MACE
was low in the tofacitinib clinical studies. The IR for MACE
in patients with PsA in the all-tofacitinib comparison cohort
was 0.4, which is the same as that reported for tofacitinib
in clinical trials in patients with RA (0.4) [47] or psoriasis (0.4)
[48] and within the range reported for other PsA therapies in
the observational comparison cohort (0.0–0.7).

In February 2019, a safety analysis of the ongoing study
A3921133 (NCT02092467), completed by the external,
independent tofacitinib Rheumatology Data Safety Moni-
toring Board, reported that the incidence of PE events was
higher in patients receiving tofacitinib 10 mg BID than in patients receiving a TNFi. Patients in the A3921133 randomized, endpoint-driven postauthorization safety study had a diagnosis of RA, were aged ≥ 50 years, and had one or more cardiovascular risk factor. Based on the safety analysis of study A3921133 and knowledge of the safety profile of other Janus kinase inhibitors [49, 50], venous thromboembolism events (including deep vein thrombosis and PE) were identified as an important risk for treatment with tofacitinib, irrespective of dose. Subsequently, thromboembolism was added as a warning and as an adverse drug reaction to the current product labeling for tofacitinib. Specifically, the updated US prescribing information includes thrombosis as a boxed warning and recommends that tofacitinib be avoided in patients at risk of thrombosis (including PE, deep vein thrombosis, and arterial thrombosis) [51], whereas the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) states that tofacitinib should be used with caution in patients with known risk factors for venous thromboembolism, regardless of indication and dosage [52].

A number of limitations of this analysis are acknowledged. Comparisons with placebo (with background csDMARDs) in this analysis were limited to the 3-month placebo-controlled portion of the phase III studies; the extent and length of exposure to placebo was therefore less. The design of the LTE study, with the optional dose adjustments between tofacitinib 5 and 10 mg BID allowed at the investigators’ discretion, prevented long-term comparison of doses. The evaluation of safety events over time was also limited by the sample size and extent of exposure; this is common in clinical trials of limited duration, and longer-term follow-up may be required. Care must be taken in interpreting data from the observational comparison cohort and comparisons of these data with the tofacitinib global clinical studies, as the comparison cohort was derived from an observational claims database, including only US-insured patients (including Medicaid). Claims reflect dispensing of medication, not necessarily actual use; medication adherence is generally higher in clinical trials than in clinical practice [53], although adherence was not confirmed by testing for drug levels in the tofacitinib clinical program. In addition, for some individual drugs such as certolizumab and apremilast, the overall patient-years of exposure for this analysis were relatively small compared with other therapies. Differences in AE reporting between the tofacitinib clinical trials and the observational comparison cohort must be noted. In the tofacitinib clinical trials, the investigator was to pursue and obtain information regarding the outcome and causality of an AE, potentially underestimating outpatient infections requiring parenteral antibiotics. In contrast, in the US Truven MarketScan database, all events were captured using administrative codes, limiting clinical detail. These differences should be taken into account when comparing the IRs of AEs between the cohorts.

5 Conclusions
In patients with active PsA, tofacitinib had a safety profile that was generally consistent with patients with PsA receiving other therapies in real-world settings. No new risks were identified compared with those observed with tofacitinib treatment of RA. As when used in RA, tofacitinib was associated with a higher risk for HZ than are most other PsA therapies. Longer-term follow-up and larger patient populations will provide further information on the safety profile of tofacitinib in patients with PsA.

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Availability of Data and Materials 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 USA and/or EU or (2) in programs 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.

Compliance with Ethical Standards

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Research involving Human Participants and/or Animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board or independent ethics committee at each investigational site and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patient data from the US Truven MarketScan database were de-identified and complied with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act. Therefore, institutional review board approval was not required.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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