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Tofacitinib in the treatment of Indian patients with rheumatoid arthritis: A post hoc analysis of efficacy and safety in Phase 3 and long-term extension studies over 7 years

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Abstract

Objectives: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We characterized tofacitinib efficacy/safety in Indian vs rest of the world (ROW; excluding India) RA patients.

Methods: Efficacy data were pooled for disease-modified antirheumatic drug (DMARD) inadequate responders from Phase (P)3 studies. For Indian patients, ORAL Solo and ORAL Scan; ROW (excluding India), these studies plus ORAL Step, ORAL Sync, and ORAL Standard. Safety data also included ORAL Start (P3; methotrexate-naïve) and ORAL Sequel (long-term extension [LTE] study; data cut-off March 2017) for Indian patients, and these studies plus A3921041 (LTE study; Japanese study) for ROW. Efficacy outcomes at months 3/6: American College of Rheumatology (ACR)20/50/70; Disease Activity Score in 28 joints, erythrocyte sedimentation rate remission/low disease activity; change from baseline in Health Assessment Questionnaire-Disability Index. Incidence rates (IRs; patients with events/100 patient-years) for adverse events of special interest (AESIs) were assessed throughout. Descriptive data underwent no formal comparison.

Results: One-hundred-and-ninety-seven Indian and 3879 ROW patients were included. Compared with ROW patients, Indian patients were younger, had lower body mass index, shorter RA duration, and higher baseline disease activity; most Indian patients were non-smokers and all were biologic DMARD (bDMARD)-naïve. Month 3 ACR20 rates with tofacitinib 5 mg twice daily/10 mg twice daily/placebo were 67.4%/82.1%/40.9% (India) and 59.0%/66.1%/28.2% (ROW), and month 6 rates were 76.2%/92.1%/88.9% (India) and 69.0%/74.2%/66.5% (ROW). Month 3/6 improvements in other outcomes were generally numerically greater with tofacitinib vs placebo, and similar in both populations. Compared with ROW, Indian patients had numerically fewer AEs/serious AEs, and similar IRs for discontinuations due to AEs

and AESIs, except that tuberculosis (TB) IR was higher in Indian (IR = 1.21; 95% CI 0.49, 2.49) vs ROW patients (IR = 0.17; 95% CI 0.11, 0.25).

Conclusions: Tofacitinib efficacy/safety were similar in both populations, except TB IR, which was higher in Indian patients but in line with those in bDMARD-treated RA patients from high-risk countries (IR = 0.00-2.56; TB IR >0.05 [World Health Organization]). Limitations included the small Indian population and baseline differences between populations.

KEYWORDS

clinical aspects, drug treatment, India, rheumatoid arthritis, tofacitinib

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disease characterized by inflammation of the articular synovium, joint damage, deformity, and progressive disability, and carries a significant burden of morbidity and economic impact.[1,2] RA has an estimated global prevalence of 0.24%.[3] However, RA receives a low level of economic support in low-to-middle income countries, such as India where age-/gender-adjusted RA prevalence is reported to be 0.34% (95% confidence interval [CI] 0.08-0.79).[4,5]

The Asia-Pacific League of Associations for Rheumatology acknowledges that treatment of RA in Asia-Pacific regions should be considered independently from the rest of the world (ROW), due to potential differences in disease prevalence/manifestation, treatment response, increased prevalence of certain infections (eg, tuberculosis [TB], hepatitis B/C) and country-specific challenges with respect to healthcare resources.[6] Filling existing gaps in our understanding of treatment responses in these countries may help to inform clinical practice.

India is among 30 countries considered to have a high TB burden, and has some of the highest global rates of TB (incidence rate [IR] = 0.2 per 100 patient-years[7]) and latent TB infection.[8] India also accounts for 23% and 36% of the global and regional burden of pneumonia, respectively.[9]

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. The clinical development program for tofacitinib includes data from 7061 patients, representing 22 875 patient-years of exposure up to 9.5 years.[10] While tofacitinib long-term extension (LTE) studies have included Asia-Pacific patients,[11-14] understanding of tofacitinib efficacy/safety in India is restricted to a post hoc analysis conducted in 8 Asia-Pacific countries (China, India, Japan, Korea, Malaysia, the Philippines, Taiwan, and Thailand; total N = 1464).[15] Efficacy outcomes for tofacitinib in this post hoc analysis of data pooled from Phase 2/3 studies were comparable with, or slightly higher than, those in global studies. Greater improvements with tofacitinib vs placebo were observed in disease activity and health status (measured by Health Assessment Questionnaire-Disability Index [HAQ-DI]) after 3 months, which persisted to 24 months. Safety outcomes (based on pooled data from Phase 2/3/LTE studies) were generally comparable with those seen in global patients; however, the infection incidence (including TB) was higher in Asia-Pacific patients.[15]

In this post hoc analysis, we characterized tofacitinib efficacy and safety in Indian patients with RA, vs patients from ROW (all patients excluding Indian patients).

2 | METHODS

2.1 | Study design and patients

This post hoc analysis pooled data from 6 double-blind, randomized controlled Phase 3 studies[16-21] and two open-label LTE studies[11,12,22] of tofacitinib in patients with RA (Table S1).

Full study details have been reported previously (summarized in Table S1). Briefly, patients were ≥18 years of age, with a diagnosis of active RA based on the American College of Rheumatology (ACR) 1987 revised criteria,[23] and had active disease at screening and baseline. Key exclusion criteria included any infection requiring antimicrobial therapy within 2 weeks prior to the first dose or history of infection requiring hospitalization or parenteral antimicrobial therapy within 6 months of randomization, history of recurrent or disseminated herpes zoster (HZ), or other opportunistic infection, evidence of active, latent, or inadequately treated *Mycobacterium tuberculosis* infection, and history of malignancy.

In Phase 3 studies, patients were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo, either alone or with background conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Patients receiving placebo advanced to tofacitinib 5 or 10 mg twice daily at month 3 or month 6. Patients in LTE studies initiated treatment with tofacitinib 5 or 10 mg twice daily, with dose adjustments permitted at the discretion of the investigator.

All studies were conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice Guidelines established by the International Conference for Harmonization. Study protocols were approved by the Institutional Review Board or Independent Ethics Committee at each center. All patients provided written informed consent.

TABLE 1 Patient demographics and baseline disease characteristics

	Phase 3 studies[a] (efficacy analysis set)					
	India			Rest of the world		
	Tofacitinib 5 mg b.i.d. (N = 51)	Tofacitinib 10 mg b.i.d. (N = 43)	Placebo (N = 26)	Tofacitinib 5 mg b.i.d. (N = 1165)	Tofacitinib 10 mg b.i.d. (N = 1171)	Placebo (N = 655)
Female, n (%)	48 (94.1)	38 (88.4)	23 (88.5)	979 (84.0)	992 (84.7)	530 (80.9)
Age, y, mean (SD)	45.4 (11.9)	47.8 (11.2)	44.2 (9.6)	53.5 (11.5)	52.7 (11.6)	52.8 (12.0)
Body weight, kg, mean (SD)	60.8 (10.9)	54.9 (10.8)	58.2 (11.6)	71.6 (20.0)	71.8 (19.1)	72.9 (21.3)
BMI, kg/m^2, mean (SD)	25.3 (5.0)	23.2 (4.2)	24.1 (4.9)	27.1 (6.8)	27.3 (6.5)	27.4 (6.9)
Race, n (%)						
White	0	0	0	737 (63.3)	741 (63.3)	439 (67.0)
Black	0	0	0	45 (3.9)	35 (3.0)	24 (3.7)
Asian	51 (100.0)	43 (100.0)	26 (100.0)	276 (23.7)	271 (23.1)	140 (21.4)
Other	0	0	0	107 (9.2)	124 (10.6)	52 (7.9)
Smoking status, n (%)						
Current smoker	0	0	0	166 (14.3)	212 (18.1)	130 (19.9)
Ex-smoker	0	0	0	242 (20.8)	194 (16.6)	124 (18.9)
Never smoked	51 (100.0)	43 (100.0)	26 (100.0)	757 (65.0)	765 (65.3)	399 (60.9)
Duration of RA, y, mean (SD)	4.1 (4.7)	6.4 (6.5)	4.4 (3.7)	8.9 (8.1)	9.2 (8.3)	9.5 (8.6)
DAS28-4(ESR), mean (SD)	7.0 (0.9)	7.1 (0.9)	7.0 (1.0)	6.4 (1.0)	6.4 (1.0)	6.4 (1.0)
CDAI, mean (SD)	43.6 (11.7)	44.3 (13.2)	41.8 (12.2)	37.2 (12.3)	36.9 (12.5)	37.1 (12.9)
HAQ-DI, mean (SD)	1.5 (0.7)	1.6 (0.6)	1.5 (0.6)	1.5 (0.7)	1.5 (0.7)	1.4 (0.7)
ESR, mm/h, mean (SD)	59.4 (29.2)	63.2 (27.8)	60.4 (30.3)	49.9 (26.1)	50.1 (26.7)	48.9 (25.2)
CRP, mg/L, mean (SD)	15.8 (28.3)	16.6 (20.2)	14.6 (15.5)	17.9 (22.2)	17.5 (22.6)	16.1 (19.2)
RF+, n (%)	31 (60.8)	35 (81.4)	21 (80.8)	821 (71.3)	814 (70.0)	437 (67.0)
Anti-CCP+, n (%)	35 (68.6)	35 (81.4)	24 (92.3)	882 (75.7)	857 (73.2)	476 (72.7)
Treatment history, n (%)						
MTX	44 (86.3)	39 (90.7)	23 (88.5)	1118 (96.0)	1115 (95.2)	626 (95.6)
csDMARDs (excluding MTX)	38 (74.5)	29 (67.4)	23 (88.5)	707 (60.7)	716 (61.1)	375 (57.3)
TNFi	0	0	0	294 (25.2)	286 (24.4)	201 (30.7)
Non-TNFi bDMARDs	0	0	0	75 (6.4)	72 (6.2)	46 (7.0)
Concomitant treatments						
MTX dose, mg/wk, mean (SD)	9.1 (9.0)	9.1 (8.5)	10.5 (8.8)	10.9 (7.5)	11.2 (7.8)	11.5 (7.7)
Glucocorticoid dose mg/d, mean (SD)	2.7 (3.0)	2.7 (3.1)	3.9 (4.1)	3.6 (3.9)	3.4 (3.8)	3.6 (4.0)

Note: N and N1 are patient numbers for both populations assessed for efficacy (Phase 3) and safety (Phase 3/LTE), respectively; the numbers of patients assessed for each endpoint may be lower than N/N1.

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; b.i.d., twice daily; BMI, body mass index; CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LTE, long-term extension; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; TDD, total daily dose; TNFi, tumor necrosis factor inhibitor; y, years.

[a]ORAL Step (NCT00960440),[16] ORAL Scan (NCT00847613),[17] ORAL Sync (NCT00856544),[19] ORAL Solo (NCT00814307),[20] and ORAL Standard (NCT00853385).[21]

[b]ORAL Step (NCT00960440),[16] ORAL Scan (NCT00847613),[17] ORAL Start (NCT01039688),[18] ORAL Sync (NCT00856544),[19] ORAL Solo (NCT00814307),[20] ORAL Standard (NCT00853385),[21] and ORAL Sequel (NCT00413699); main study database locked at time of analysis: March 2, 2017),[12,22] and Study A3921041 (NCT00661661); Japanese study.[11]

[c]Includes all patients receiving tofacitinib in Phase 3 and LTE studies.

[d]The average TDD of tofacitinib for each patient was calculated as the sum of all doses received divided by the number of days of treatment over the entire study duration for each patient; average tofacitinib doses of 5 mg b.i.d. and 10 mg b.i.d. were defined as TDD <15 mg b.i.d. and TDD ≥15 mg b.i.d., respectively.

Phase 3/LTE[b] (safety analysis set)[c]					
India			Rest of the world		
Average tofacitinib 5 mg b.i.d. (N1 = 58) [d]	Average tofacitinib 10 mg b.i.d. (N1 = 139) [d]	All tofacitinib (N1 = 197)	Average tofacitinib 5 mg b.i.d. (N1 = 1005)	Average tofacitinib 10 mg b.i.d. (N1 = 2874) [d]	All tofacitinib (N1 = 3879)
48 (82.8)	125 (89.9)	173 (87.8)	838 (83.4)	2366 (82.3)	3204 (82.6)
43.3 (13.1)	44.9 (10.6)	44.4 (11.4)	53.3 (12.2)	52.1 (11.7)	52.4 (11.8)
59.6 (12.5)	57.1 (11.4)	57.8 (11.8)	69.3 (18.5)	73.0 (19.5)	72.0 (19.3)
24.5 (5.6)	23.8 (4.5)	24.0 (4.9)	26.5 (6.3)	27.4 (6.5)	27.1 (6.4)
0	0	0	529 (52.6)	2055 (71.5)	2584 (66.6)
0	1 (<1.0)	1 (<1.0)	31 (3.1)	98 (3.4)	129 (3.3)
58 (100)	138 (99.3)	196 (99.5)	354 (35.2)	401 (14.0)	755 (19.5)
0	0	0	91 (9.1)	320 (11.1)	411 (10.6)
0	1 (<1.0)	1 (<1.0)	143 (14.2)	545 (19.0)	688 (17.7)
0	0	0 (0.0)	195 (19.4)	495 (17.2)	690 (17.8)
58 (100)	138 (99.3)	196 (99.5)	667 (66.4)	1831 (63.7)	2498 (64.4)
2.6 (3.1)	4.0 (5.0)	3.6 (4.6)	7.9 (8.0)	7.8 (8.1)	7.8 (8.1)
7.1 (0.9)	7.1 (0.9)	7.1 (0.9)	6.4 (1.0)	6.4 (1.0)	6.4 (1.0)
43.4 (12.2)	42.9 (13.5)	43.1 (13.1)	36.5 (12.7)	37.6 (12.3)	37.3 (12.5)
1.6 (0.6)	1.6 (0.6)	1.6 (0.6)	1.5 (0.7)	1.5 (0.7)	1.5 (0.7)
64.2 (30.9)	66.6 (29.3)	65.9 (29.8)	51.0 (25.3)	50.0 (26.5)	50.3 (26.2)
20.4 (29.9)	19.0 (22.2)	19.4 (24.6)	18.1 (22.3)	18.3 (23.1)	18.2 (22.9)
42 (73.7)	113 (81.9)	155 (79.5)	741 (74.5)	2043 (71.6)	2784 (72.3)
46 (79.3)	117 (84.8)	163 (83.2)	793 (79.4)	2152 (75.6)	2945 (76.6)
30 (51.7)	73 (52.5)	103 (52.3)	798 (79.4)	2203 (76.7)	3001 (77.4)
40 (69.0)	96 (69.1)	136 (69.0)	603 (60.0)	1562 (54.3)	2165 (55.8)
0	0	0	80 (8.0)	140 (4.9)	220 (5.7)
0	0	0	49 (4.9)	142 (4.9)	191 (4.9)
5.9 (8.4)	5.3 (8.1)	5.5 (8.2)	9.2 (7.6)	8.9 (8.4)	9.0 (8.2)
3.9 (3.1)	5.0 (17.4)	4.6 (14.7)	3.5 (4.0)	3.3 (4.2)	3.4 (4.1)

2.2 | Post hoc analysis of efficacy and safety in Indian vs ROW populations

Efficacy analyses were based on pooled data from csDMARD and biologic (b)DMARD inadequate responders (csDMARD-IR and bDMARD-IR, respectively) enrolled in Phase 3 studies. The Indian population comprised patients in ORAL Scan and ORAL Solo. The ROW efficacy population included patients in ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync, and ORAL Standard.

Efficacy outcomes were evaluated at months 3 and 6, and included the proportion of patients achieving 20%, 50%, or 70% improvement in ACR criteria (ACR20/50/70 response rates, respectively); the proportion of patients achieving Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4[ESR])-defined remission (<2.6) or low disease activity (≤3.2); and change from baseline in HAQ-DI.

Safety analyses were based on data from patients who received ≥1 dose of tofacitinib in Phase 3/LTE studies. Indian patients were enrolled in ORAL Scan, ORAL Solo, ORAL Start, and ORAL Sequel. ROW data were pooled from ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync, ORAL Start, ORAL Standard, ORAL Sequel, and A3921041.

Safety analyses included adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs, confirmed laboratory abnormalities (based on two sequential measurements), mortality rates and IRs (patients with events per 100 patient-years) for AEs of special interest (AESIs; TB, interstitial lung disease [ILD], opportunistic infections, HZ, serious infection events [SIEs], major adverse cardiovascular events [MACE], malignancies excluding non-melanoma skin cancer [NMSC], lymphoma and lymphoproliferative disorders, and gastrointestinal [GI] perforations). In addition, the Data Safety Monitoring Board for tofacitinib rheumatology studies recently determined that the frequency of pulmonary embolism (PE) in the tofacitinib 10 mg twice daily arm was higher than the frequency of PE in the tumor necrosis factor inhibitor (TNFi) comparator arm in a US Food and Drug Administration post-marketing requirement safety study (A3921133; NCT02092467),[24] designed to evaluate the long-term risk of MACE and malignancy. Study A3921133 is an ongoing, open-label, endpoint-driven study, evaluating the safety of tofacitinib 5 and 10 mg twice daily, compared with TNFi in patients with RA. Patients had to be ≥50 years of age, have ≥1 cardiovascular risk factor, and be on a stable dose of methotrexate (MTX) to be eligible for enrollment. Subsequently, based on information from Study A3921133 and consideration of information pertaining to PE for other JAK inhibitors, Pfizer has determined that PE is an important potential risk for treatment with tofacitinib. Therefore, incidence of venous thromboembolic events (VTE, including PE or deep vein thrombosis) was also assessed in the present analysis.

SAEs were defined as any AEs that were life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability, incapacity or congenital birth defects, or death.

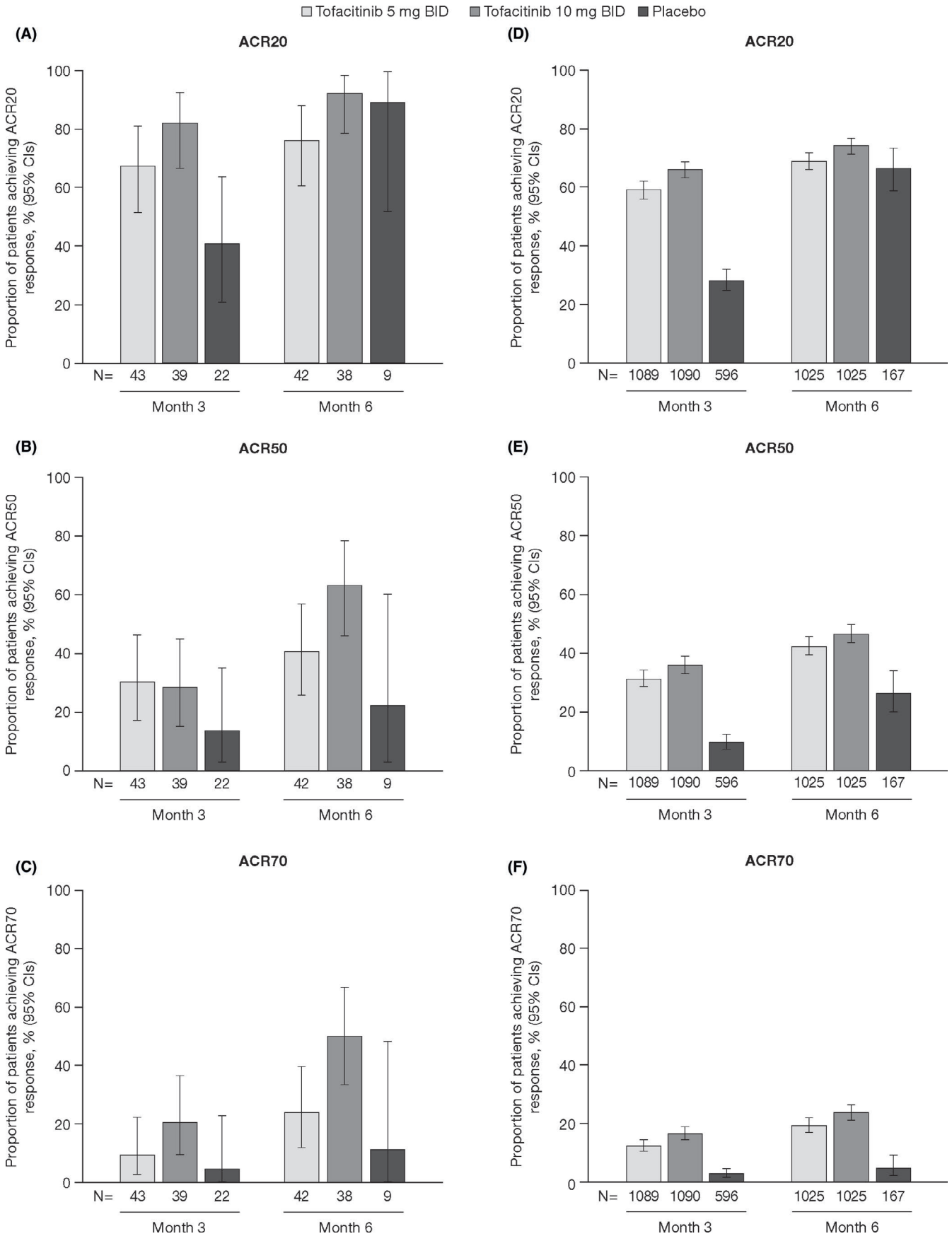
Screening for latent TB infection was carried out using QuantiFERON-GOLD®™ or Mantoux purified protein derivative tuberculin skin tests at baseline of Phase 3 studies, unless tested and documented within 3 months of the screening visit. Patients with latent TB infections were permitted to enroll in the study; however, those with untreated/inadequately treated latent TB infections had to enroll after ≥1 month of isoniazid treatment. Per protocol, regular QuantiFERON-GOLD®™ testing was performed post-baseline in patients from countries with a TB prevalence of >50 cases per 100 000 persons (eg, India)[7] who were negative for latent TB infection at baseline. Follow-up chest radiographs were required for patients with positive latent TB infection results post-baseline; only those without active TB infection by chest radiograph were allowed to continue.

2.3 | Statistical analysis

Efficacy analyses were based on the full analysis set, which included all patients who received ≥1 dose of study drug for whom data were available from ≥1 post-baseline assessment. Treatment differences were assessed using 95% CI, calculated using the Clopper-Pearson (Exact) method and *t* statistics for binary and continuous endpoints, respectively. Treatments were considered different if 95% CI did not overlap, or numerically different if 95% CI marginally overlapped. Baseline was defined as the start of the qualifying index study for patients enrolled in Phase 3 studies; for patients in LTE studies, baseline was defined as the start of the qualifying index study for patients enrolling within ≤14 days of index study completion, or the start of the LTE for patients enrolling >14 days after index study completion.

Safety endpoints were reported throughout each study, and were based on all treated patients who received ≥1 dose of study drug. IRs and 95% CI, calculated via the Exact Poisson method adjusted for exposure time, were based on the number of unique patients with first events occurring between first and last dose plus 28 days, divided by the time accrued during the risk period (ie between first and last dose plus 28 days, or the time accrued to the first event, whichever occurred earlier).

FIGURE 1 The proportion of Indian patients achieving (A) ACR20, (B) ACR50, and (C) ACR70 responses at months 3 and 6; and the proportion of ROW patients achieving (D) ACR20, (E) ACR50, and (F) ACR70 responses at months 3 and 6. Patients receiving placebo in ORAL Solo and ORAL Step advanced in a blinded manner to tofacitinib 5 or 10 mg b.i.d. at month 3; placebo-treated non-responders (defined as patients not achieving ≥20% reduction from baseline in swollen and tender joint counts) in ORAL Scan, ORAL Sync, and ORAL Standard advanced in a blinded manner to tofacitinib 5 or 10 mg b.i.d. at month 3; remaining placebo-treated patients advanced at month 6; efficacy analyses were based on observed cases without imputation for missing data; all endpoints are reported by descriptive statistics with no formal hypothesis testing. ACR, American College of Rheumatology; b.i.d., twice daily; CI, confidence interval; ROW, rest of the world


Tofacitinib 5 mg BID
Tofacitinib 10 mg BID
Placebo
(A)
ACR20
Proportion of patients achieving ACR20 response, % (95% CIs)
100
80
60
40
20
0
N= 43 39 22 42 38 9
Month 3
Month 6
(D)
ACR20
Proportion of patients achieving ACR20 response, % (95% CIs)
N= 1089 1090 596 1025 1025 167
Month 3
Month 6
(B)
ACR50
Proportion of patients achieving ACR50 response, % (95% CIs)
N= 43 39 22 42 38 9
Month 3
Month 6
(E)
ACR50
Proportion of patients achieving ACR50 response, % (95% CIs)
N= 1089 1090 596 1025 1025 167
Month 3
Month 6
(C)
ACR70
Proportion of patients achieving ACR70 response, % (95% CIs)
N= 43 39 22 42 38 9
Month 3
Month 6
(F)
ACR70
Proportion of patients achieving ACR70 response, % (95% CIs)
N= 1089 1090 596 1025 1025 167
Month 3
Month 6

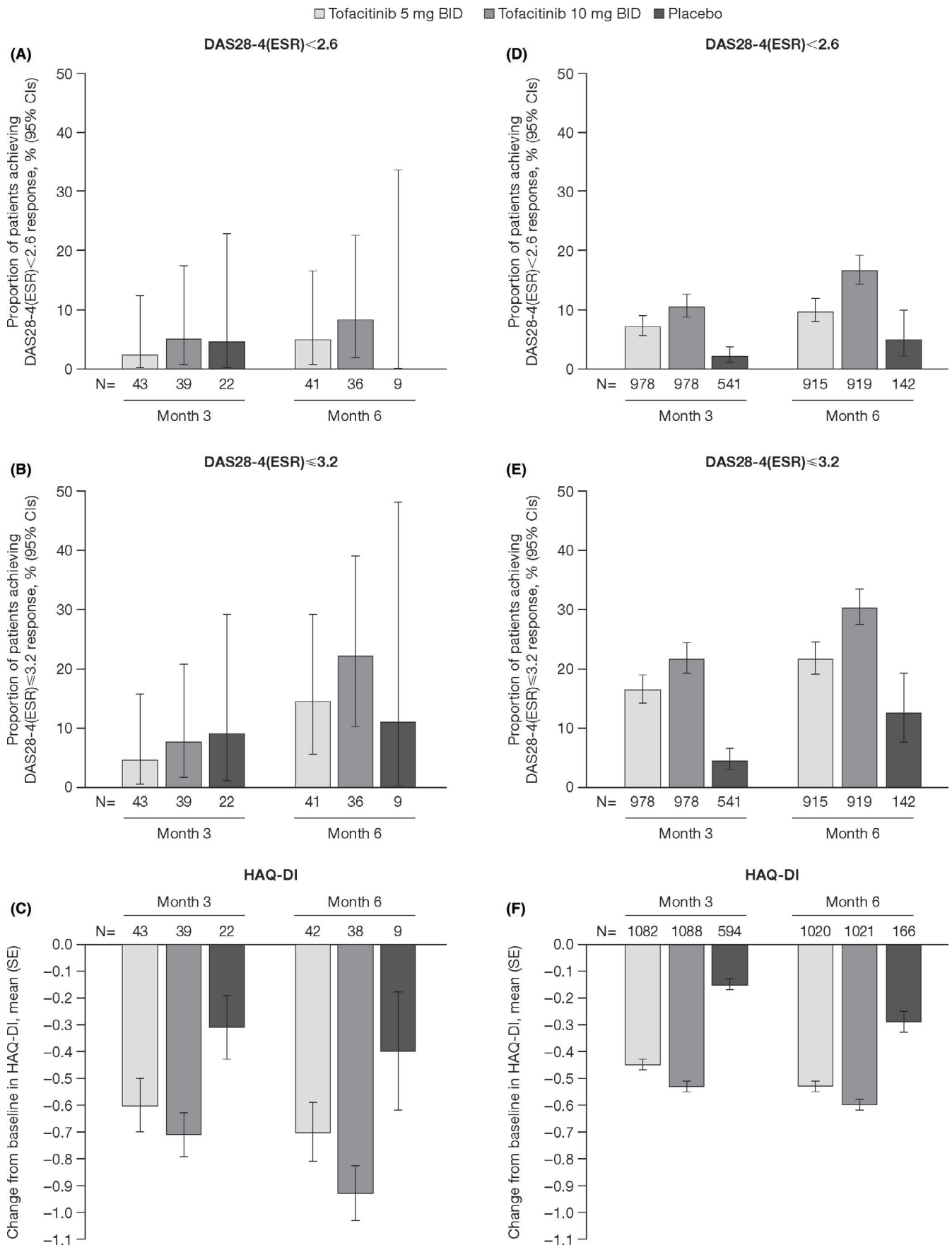

Tofacitinib 5 mg BID
Tofacitinib 10 mg BID
Placebo
(A)
DAS28-4(ESR)<2.6
Proportion of patients achieving DAS28-4(ESR)<2.6 response, % (95% CIs)
N= 43 39 22 41 36 9
Month 3
Month 6
(D)
DAS28-4(ESR)<2.6
Proportion of patients achieving DAS28-4(ESR)<2.6 response, % (95% CIs)
N= 978 978 541 915 919 142
Month 3
Month 6
(B)
DAS28-4(ESR)≤3.2
Proportion of patients achieving DAS28-4(ESR)≤3.2 response, % (95% CIs)
N= 43 39 22 41 36 9
Month 3
Month 6
(E)
DAS28-4(ESR)≤3.2
Proportion of patients achieving DAS28-4(ESR)≤3.2 response, % (95% CIs)
N= 978 978 541 915 919 142
Month 3
Month 6
(C)
HAQ-DI
Month 3
Month 6
N= 43 39 22 42 38 9
Change from baseline in HAQ-DI, mean (SE)
(F)
HAQ-DI
Month 3
Month 6
N= 1082 1088 594 1020 1021 166
Change from baseline in HAQ-DI, mean (SE)

FIGURE 2 The proportion of Indian patients achieving (A) DAS28-4(ESR) <2.6, (B) DAS28-4(ESR) ≤3.2, and (C) change from baseline in HAQ-DI, at months 3 and 6; and the proportion of ROW patients achieving (D) DAS28-4(ESR) <2.6, (E) DAS28-4(ESR) ≤3.2, and (F) change from baseline in HAQ-DI, at months 3 and 6. Patients receiving placebo in ORAL Solo and ORAL Step advanced in a blinded manner to tofacitinib 5 or 10 mg b.i.d. at month 3; placebo-treated non-responders (defined as patients not achieving ≥20% reduction from baseline in swollen and tender joint counts) in ORAL Scan, ORAL Sync, and ORAL Standard advanced in a blinded manner to tofacitinib 5 or 10 mg b.i.d. at month 3; remaining placebo-treated patients advanced at month 6; efficacy analyses were based on observed cases without imputation for missing data. b.i.d., twice daily; CI confidence interval; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; ROW, rest of the world; SE, standard error

All analyses were based on observed cases without imputation for missing data. No multiplicity adjustment was made for any comparisons.

3 | RESULTS

3.1 | Patients

The safety analysis set included 197 patients from India and 3879 ROW patients (total exposure [all tofacitinib doses], 564.2 patient-years and 14 279.9 patient-years in Indian and ROW patients, respectively). The efficacy analysis set included 51 Indian patients receiving tofacitinib 5 mg twice daily (total exposure, 51.7 patient-years), 43 Indian patients receiving tofacitinib 10 mg twice daily (total exposure, 49.2 patient-years), and 26 Indian patients receiving placebo (total exposure, 8.7 patient-years); and 1165 ROW patients receiving tofacitinib 5 mg twice daily (total exposure, 1081.2 patient-years), 1171 ROW patients receiving tofacitinib 10 mg twice daily (total exposure, 1099.1 patient-years), and 655 ROW patients receiving placebo (total exposure, 194.0 patient-years).

Patient demographics and baseline disease characteristics are shown in Table 1. Some numerical differences were observed between populations. Indian patients were younger, had lower body weight, lower body mass index (BMI), shorter disease duration, higher baseline disease activity, and were more likely to be non-smokers, compared with patients from ROW. Prior treatment for Indian patients predominantly comprised non-MTX csDMARDs, and no Indian patients previously received bDMARDs. ROW patients had mostly received MTX and some ROW patients had previously received bDMARDs.

3.2 | Efficacy at months 3 and 6

ACR20, ACR50, and ACR70 response rates for the Indian population are shown in Figure 1A-C respectively; ACR20, AC50, and ACR70 response rates for the ROW population are shown in Figure 1D-F respectively. At month 6, ACR20 response rates were 76.2%, 92.1%, and 88.9% in Indian patients, and 69.0%, 74.2%, and 66.5% in ROW patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo, respectively (Figure 1A,D).

In Indian patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, ACR50 response rates at months 3 and 6 were 30.2%/28.2%/13.6% and 40.5%/63.2%/22.2%, respectively; and ACR70 response rates were 9.3%/20.5%/4.6% and 23.8%/50.0%/11.1% at months 3 and 6, respectively. In ROW patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, ACR50 response rates at months 3 and 6 were 31.1%/35.7%/9.7% and 42.2%/46.4%/26.4%, respectively; and ACR70 response rates were 12.4%/16.5%/2.9% and 19.3%/23.8%/4.8% at months 3 and 6, respectively (Figure 1B,C,E,F).

The proportions of Indian patients achieving DAS28-4(ESR) remission or low disease activity are shown in Figure 2A,B, respectively; change from baseline in HAQ-DI in Indian patients is shown in Figure 2C. The proportions of ROW patients achieving DAS28-4(ESR) remission or low disease activity, and change from baseline in HAQ-DI in ROW patients, is shown in Figure 2D-F respectively.

In Indian patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, the proportions achieving DAS28-4(ESR) remission at months 3 and 6 were 2.3%/5.1%/4.6% and 4.9%/8.3%/0.0%, respectively; and DAS28-4(ESR) low disease activity was achieved by 4.7%/7.7%/9.1% and 14.6%/22.2%/11.1% at months 3 and 6, respectively. In ROW patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, rates of DAS28-4(ESR) remission at months 3 and 6 were 7.2%/10.4%/2.0% and 9.7%/16.7%/4.9%, respectively; and DAS28-4(ESR) low disease activity rates were 16.6%/21.8%/4.4% and 21.8%/30.5%/12.7% at months 3 and 6, respectively (Figure 2D,E).

In Indian patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, change from baseline in HAQ-DI at months 3 and 6 was -0.60/-0.71/-0.31 and -0.70/-0.93/-0.40, respectively (Figure 2C). In ROW patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, change from baseline in HAQ-DI at months 3 and 6 was -0.45/-0.53/-0.15 and -0.53/-0.60/-0.29 respectively (Figure 2F).

3.3 | Safety

Safety data from pooled Phase 3/LTE studies are summarized in Table 2. A lower proportion of Indian patients experienced AEs, compared with ROW patients (36.0% vs 50.3% respectively, up to month 3; 23.4% vs 38.4%, respectively, from months 3-6; 60.9% vs 79.5%, respectively, post-month 6). Likewise, Indian patients were less likely to experience SAEs, compared with ROW patients (15.7% vs 29.3%, respectively). Rates of discontinuations due to AEs were similar in both populations. Incidence of mortality was also similar between Indian and ROW patients (IR = 0.17 per 100 patient-years; 95% CI 0.00-0.96 vs IR = 0.23 per 100 patient-years; 95% CI 0.16-0.32, respectively).

Considering AESIs, the incidence of ILD, opportunistic infections excluding TB, HZ, SIEs, MACE, malignancies excluding NMSC, lymphoma, and GI perforations were similar between Indian and ROW patients. Of these, HZ (IR = 2.93, 95% CI 1.67-4.76 and IR = 3.62, 95% CI 3.31-3.96 per 100 patient-years, for Indian and ROW patients, respectively) and SIEs (IR = 2.59, 95% CI 1.45-4.28 and IR = 2.47, 95% CI 2.22-2.74 per 100 patient-years, for Indian and ROW patients, respectively) were of the highest incidence; others had an IR of <0.8 per 100 patient-years. There were no cases of VTE in Indian patients in the safety analysis set.

TB rates were higher in Indian vs ROW patients. TB incidence in the Indian population was 1.21 per 100 patient-years (based on seven events overall; three events in Phase 3 studies, and four events in LTE studies; all patients were receiving 10 mg twice daily at onset). In contrast, TB IR in ROW patients was 0.17 per 100 patient-years (based on 25 events overall; six events in Phase 3 studies [all patients were receiving 10 mg twice daily at onset], and 19 events in LTE studies [three patients were receiving 5 mg twice daily and 16 patients were receiving 10 mg twice daily at onset]). Mean time to onset of TB was shorter in Indian vs ROW patients (635.1 days vs 725.8 days, respectively).

In total, 23 Indian patients had latent TB infections at baseline of Phase 3 studies, which was adequately treated in 14 patients, and untreated/inadequately treated in nine patients. In the ROW population, 216 patients had latent TB infections at Phase 3 baseline, which was adequately treated in 200 patients and untreated/inadequately treated in 16 patients. No Indian patients with latent TB infections developed TB during Phase 3/LTE studies. However, in the subgroup of ROW patients with latent TB infections, four patients developed TB; one case occurred during Phase 3 studies and three cases occurred during LTE studies. All of these patients were receiving tofacitinib 10 mg twice daily at the time of the event, and all were previously adequately treated for latent TB infections. In addition, there were 31 patients from high-risk TB countries (including five Indian patients) with no evidence of latent TB at baseline, but who subsequently tested positive for latent TB infection post-baseline (of these, 26 patients were negative for latent TB infection at baseline, three patients had an indeterminate infection status, and two patients were not tested). However, none of these patients had active TB, as assessed by follow-up chest radiogram.

A summary of confirmed laboratory abnormalities is shown in Table 3. IRs for laboratory abnormalities were generally similar in Indian and ROW patients, except for lymphocyte counts ≥1.5-<2 × 1000/mm^3, which were higher in Indian vs ROW patients, and lymphocyte counts ≥0.5-<1.5 × 1000/mm^3 and increases in alanine aminotransferase (ALT) >1 × upper limit of normal (ULN), which were lower in Indian vs ROW patients.

4 | DISCUSSION

In this post hoc analysis, we present a comprehensive characterization of the efficacy and safety of tofacitinib in Indian and ROW patients with RA enrolled in Phase 3 and LTE studies. This fills an important gap in knowledge regarding tofacitinib treatment in this country of high RA burden.

In this post hoc analysis of data from Phase 3 and LTE studies of tofacitinib, numerical differences were observed between the Indian and ROW populations; however, patient numbers were low, 95% CIs were large in the Indian population, and endpoints were reported descriptively, which should be taken into consideration when interpreting the results. Compared with ROW patients, Indian patients were younger, had lower body weight, lower BMI, shorter disease duration, and higher baseline disease activity. In addition, unlike ROW patients, most Indian patients were non-smokers and all were bDMARD-naïve. We observed that improvements in efficacy outcomes at months 3 and 6 were generally numerically similar in Indian vs ROW patients, and, in general, tofacitinib was superior to placebo. Efficacy was generally numerically greater with tofacitinib 10 mg twice daily vs 5 mg twice daily in ROW patients, but comparable with both tofacitinib doses in Indian patients.

Overall, AE and SAE rates were lower in Indian vs ROW patients, but discontinuations due to AEs were similar between populations. One possible explanation for this observation is that Indian patients may discontinue medications sooner than ROW patients, as it would be expected that the likelihood of developing a treatment-emergent AE would increase with longer treatment exposure, whereas, conversely, patients who discontinue sooner would be expected to be at a lower risk of treatment-emergent complications. To date, no analyses of discontinuation rates have been carried out in Indian patients with RA; however, it has previously been reported that patients of South Asian origin have lower self-reported drug adherence rates, and may discontinue RA medications early, compared with British/North European patients with RA,[25,26] which may be due to negative beliefs about medicines, problems with effective communication, and cultural differences in attitudes to chronic illness in patients of South Asian origin.[26,27]

The incidence of AESIs was generally low (IR <0.8 per 100 patient-years) in both populations, aside from HZ (India: IR = 2.93 per 100 patient-years; ROW: IR = 3.62 per 100 patient-years), SIEs (India: IR = 2.59 per 100 patient-years; ROW: IR = 2.47 per 100 patient-years), and TB (India: IR = 1.21 per 100 patient-years; ROW: IR = 0.17 per 100 patient-years). Of these, the incidence of TB was greater in Indian vs ROW patients, which may reflect the higher background incidence of TB in India.[7] In addition, higher BMI has been shown to be associated with a reduced TB risk,[28,29] and Indian patients in this analysis had lower body weight and BMI compared with the ROW population, which may have also influenced the increased TB IR in the Indian cohort.

There were no cases of VTE in the Indian population. In this analysis, Indian patients were younger and had lower BMI, compared with ROW patients. Older age and obesity are known risk factors for VTE,[30] and, in addition, obesity has been shown to be a time-dependent risk factor for VTEs in patients with RA.[31] Furthermore, unlike ROW patients, no Indian patients in this analysis had prior bDMARD experience. It has previously been reported that

TABLE 2 Summary of safety

	India			Rest of the world		
	Average tofacitinib 5 mg b.i.d. (N = 58) [a]	Average tofacitinib 10 mg b.i.d. (N = 139) [a]	All tofacitinib (N = 197)	Average tofacitinib 5 mg b.i.d. (N = 1005) [a]	Average tofacitinib 10 mg b.i.d. (N = 2874) [a]	All tofacitinib (N = 3879)
Total tofacitinib exposure, patient-y	90.9	473.3	564.2	2521.0	11 758.9	14 279.9
Tofacitinib treatment duration, y, mean (SD)	1.6 (1.4)	3.4 (2.2)	2.9 (2.2)	2.5 (2.0)	4.1 (2.2)	3.7 (2.3)
Patients with treatment-emergent AEs, n (%)						
Up to month 3	25 (43.1)	46 (33.1)	71 (36.0)	503 (50.0)	1450 (50.5)	1953 (50.3)
Months 3-6	17 (29.3)	29 (20.9)	46 (23.4)	375 (37.3)	1115 (38.8)	1490 (38.4)
Post-month 6	31 (53.4)	89 (64.0)	120 (60.9)	668 (66.5)	2416 (84.1)	3084 (79.5)
Patients with discontinuations due to AEs, n (%)	19 (32.8)	29 (20.9)	48 (24.4)	294 (29.3)	699 (24.3)	993 (25.6)
Patients with SAEs, n (%)	11 (19.0)	20 (14.4)	31 (15.7)	256 (25.5)	881 (30.7)	1137 (29.3)
Patients with mortality within 30 d, all-cause, n (%); IR (95% CI)	1 (1.7) 1.05 (0.03-5.84)	0 (0.0) 0.00 (0.00-0.76)	1 (0.5) 0.17 (0.00-0.96)	12 (1.2) 0.46 (0.24-0.81)	21 (0.7) 0.18 (0.11-0.27)	33 (0.9) 0.23 (0.16-0.32)
Patients with AESIs, n (%); IR (95% CI)						
TB[b]	1 (1.7) 1.05 (0.03-5.85)	6 (4.3) 1.24 (0.45-2.69)	7 (3.6)[c] 1.21 (0.49-2.49)	4 (0.4) 0.15 (0.04-0.39)	21 (0.7) 0.18 (0.11-0.27)	25 (0.6)[d] 0.17 (0.11-0.25)
ILD	0 (0.0) 0.00 (0.00-3.87)	1 (0.7) 0.21 (0.01-1.16)	1 (0.5) 0.17 (0.00-0.97)	5 (0.5) 0.19 (0.06-0.45)	21 (0.7) 0.18 (0.11-0.27)	26 (0.7) 0.18 (0.12-0.26)
Opportunistic infections, excluding TB[b]	0 (0.0) 0.00 (0.00-3.87)	1 (0.7) 0.21 (0.01-1.16)	1 (0.5) 0.17 (0.00-0.96)	12 (1.2) 0.46 (0.24-0.81)	43 (1.5) 0.36 (0.26-0.48)	55 (1.4) 0.38 (0.28-0.49)
HZ	3 (5.2) 3.20 (0.66-9.35)	13 (9.4) 2.87 (1.53-4.91)	16 (8.1) 2.93 (1.67-4.76)	92 (9.2) 3.82 (3.08-4.69)	394 (13.7) 3.58 (3.24-3.95)	486 (12.5) 3.62 (3.31-3.96)
Serious infections	7 (12.1) 7.47 (3.00-15.39)	8 (5.8) 1.65 (0.71-3.25)	15 (7.6) 2.59 (1.45-4.28)	91 (9.1) 3.52 (2.84-4.33)	266 (9.3) 2.24 (1.98-2.53)	357 (9.2) 2.47 (2.22-2.74)
MACE[b]	0 (0.0) 0.00 (0.00-3.87)	0 (0.0) 0.00 (0.00-0.76)	0 (0.0) 0.00 (0.00-0.64)	7 (0.7) 0.27 (0.11-0.56)	10 (0.3) 0.08 (0.04-0.15)	17 (0.4) 0.12 (0.07-0.19)

(Continues)

TABLE 2 (Continued)

	India			Rest of the world		
	Average tofacitinib 5 mg b.i.d. (N = 58) [a]	Average tofacitinib 10 mg b.i.d. (N = 139) [a]	All tofacitinib (N = 197)	Average tofacitinib 5 mg b.i.d. (N = 1005) [a]	Average tofacitinib 10 mg b.i.d. (N = 2874) [a]	All tofacitinib (N = 3879)
Malignancies (excl. NMSC)[b]	1 (1.7) 1.05 (0.03-5.84)	0 (0.0) 0.00 (0.00-0.76)	1 (0.5) 0.17 (0.00-0.96)	23 (2.3) 0.88 (0.56-1.33)	88 (3.1) 0.73 (0.59-0.91)	111 (2.9) 0.76 (0.63-0.92)
Lymphoma and lymphoproliferative disorders[b]	0 (0.0) 0.00 (0.00-3.87)	0 (0.0) 0.00 (0.00-0.76)	0 (0.0) 0.00 (0.00-0.64)	0 (0.0) 0.00 (0.00-0.14)	9 (0.3) 0.08 (0.03-0.14)	9 (0.2) 0.06 (0.03-0.12)
GI perforations[b]	0 (0.0) 0.00 (0.00-3.87)	0 (0.0) 0.00 (0.00-0.76)	0 (0.0) 0.00 (0.00-0.64)	1 (0.1) 0.04 (0.00-0.21)	13 (0.05) 0.11 (0.06-0.19)	14 (0.4) 0.10 (0.05-0.16)
Mean (SD) time to onset of TB, d	974.0 (0.0)	578.7 (532.0)	635.1 (508.1)	638.2 (255.7)	747.8 (486.1)	725.8 (447.2)

Note: N are patient numbers for both populations in the safety analysis set; n are number of patients with an event; IRs are patients with events per 100 patient-years; for the Indian population, safety data were pooled from ORAL Scan, ORAL Solo, ORAL Start, and LTE study ORAL Sequel; ROW safety data were pooled from ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync, ORAL Start, ORAL Standard, ORAL Sequel, and A3921041.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; b.i.d., twice daily; CI, confidence interval; GI, gastrointestinal; HZ, herpes zoster; ILD, interstitial lung disease; IR, incidence rate; LTE, long-term extension; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; ROW, rest of the world; SAE, serious adverse event; SD, standard deviation; TB, tuberculosis; TDD, total daily dose.

[a]The average TDD of tofacitinib for each patient was calculated as the sum of all doses received divided by number of days of treatment over the entire study duration for each patient; average tofacitinib doses of 5 mg b.i.d. and 10 mg b.i.d. were defined as TDD <15 mg b.i.d. and TDD ≥15 mg b.i.d., respectively.

[b]Adjudicated event.

[c]For 7 TB cases in the Indian population, Phase 3: n = 3, LTE: n = 4 (all patients were receiving tofacitinib 10 mg b.i.d. at onset).

[d]For 25 TB cases in the ROW population, Phase 3: n = 6 (all patients were receiving tofacitinib 10 mg b.i.d. at onset), LTE: n = 19 (3 patients were receiving tofacitinib 5 mg b.i.d. and 16 patients were receiving tofacitinib 10 mg b.i.d. at onset).

TABLE 3 Confirmed laboratory abnormalities

n (%); IR (95% CI)	India			Rest of the world		
	Average tofacitinib 5 mg b.i.d. (N = 58) [a]	Average tofacitinib 10 mg b.i.d. (N = 139) [a]	All tofacitinib (N = 197)	Average tofacitinib 5 mg b.i.d. (N = 1005) [a]	Average tofacitinib 10 mg b.i.d. (N = 2874) [a]	All tofacitinib (N = 3879)
ALT, IU/L						
>1 × ULN	8 (13.8) 10.33 (4.46-20.35)	14 (10.1) 3.14 (1.72-5.27)	22 (11.2) 4.21 (2.64-6.37)	204 (20.3) 10.06 (8.73-11.54)	654 (22.8) 6.83 (6.32-7.38)	858 (22.1) 7.40 (6.91-7.91)
>2 × ULN	2 (3.4) 2.22 (0.27-8.01)	7 (5.0) 1.53 (0.62-3.15)	9 (4.6) 1.64 (0.75-3.12)	40 (4.0) 1.65 (1.18-2.24)	106 (3.7) 0.93 (0.76-1.12)	146 (3.8) 1.05 (0.89-1.24)
>3 × ULN	1 (1.7) 1.10 (0.03-6.13)	2 (1.4) 0.42 (0.05-1.53)	3 (1.5) 0.53 (0.11-1.55)	27 (2.7) 1.08 (0.71-1.58)	69 (2.4) 0.59 (0.46-0.75)	96 (2.5) 0.68 (0.55-0.83)
AST, IU/L						
>1 × ULN	8 (13.8) 10.05 (4.34-19.79)	16 (11.5) 3.75 (2.14-6.09)	24 (12.2) 4.74 (3.04-7.05)	198 (19.7) 9.59 (8.30-11.02)	655 (22.8) 6.73 (6.22-7.26)	853 (22.0) 7.23 (6.75-7.73)
>2 × ULN	1 (1.7) 1.10 (0.03-6.13)	4 (2.9) 0.86 (0.23-2.20)	5 (2.5) 0.90 (0.29-2.10)	25 (2.5) 1.00 (0.65-1.48)	58 (2.0) 0.50 (0.38-0.64)	83 (2.1) 0.59 (0.47-0.73)
>3 × ULN	0 (0.0) 0.00 (0.00-4.06)	2 (1.4) 0.42 (0.05-1.53)	2 (1.0) 0.35 (0.04-1.28)	13 (1.3) 0.52 (0.28-0.88)	28 (1.0) 0.24 (0.16-0.35)	41 (1.1) 0.29 (0.21-0.39)
Hb, g/dL						
≥1-≤2 decrease	7 (12.1) 8.15 (3.28-16.79)	24 (17.3) 5.73 (3.67-8.52)	31 (15.7) 6.14 (4.17-8.71)	138 (13.7) 6.15 (5.17-7.27)	583 (20.3) 5.83 (5.37-6.33)	721 (18.6) 5.89 (5.47-6.34)
>2-<3 decrease; or Hb >7-<8	2 (3.4) 2.21 (0.27-7.98)	11 (7.9) 2.44 (1.22-4.36)	13 (6.6) 2.40 (1.28-4.10)	26 (2.6) 1.05 (0.69-1.54)	139 (4.8) 1.20 (1.01-1.42)	165 (4.3) 1.18 (1.01-1.37)
≥3 decrease; or Hb ≤7	0 (0.0) 0.00 (0.00-4.06)	0 (0.0) 0.00 (0.00-0.78)	0 (0.0) 0.00 (0.00-0.65)	6 (0.6) 0.24 (0.09-0.52)	54 (1.9) 0.46 (0.35-0.60)	60 (1.5) 0.42 (0.32-0.54)
Serum creatinine, ≥50% increase from baseline, mg/dL	6 (10.3) 17.18 (2.63-15.63)	0 (0.0) NA	6 (3.0) 1.08 (0.40-2.34)	53 (5.3) 2.20 (1.65-2.87)	166 (5.8) 1.46 (1.25-1.70)	219 (5.6) 1.59 (1.38-1.81)
Lymphocyte count, (×1000/mm^3) [b]						
≥1.5-<2	10 (17.2) 13.63 (6.54-25.07)	39 (28.1) 9.78 (6.95-13.37)	49 (24.9) 10.38 (7.68-13.72)	197 (19.6) 8.65 (7.48-9.94)	525 (18.3) 4.91 (4.50-5.35)	722 (18.6) 5.57 (5.17-5.99)
≥0.5-<1.5	20 (34.5) 31.23 (19.07-48.23)	81 (58.3) 32.64 (25.92-40.57)	101 (51.3) 32.35 (26.35-39.31)	595 (59.2) 57.97 (53.40-62.82)	1993 (69.3) 39.32 (37.61-41.08)	2588 (66.7) 42.46 (40.84-44.13)
<0.5	0 (0.0) 0.00 (0.00-4.06)	0 (0.0) 0.00 (0.00-0.78)	0 (0.0) 0.00 (0.00-0.65)	9 (0.9) 0.36 (0.16-0.68)	45 (1.6) 0.38 (0.28-0.51)	54 (1.4) 0.38 (0.29-0.50)

(Continues)

TABLE 3 (Continued)

n (%); IR (95% CI)	India			Rest of the world		
	Average tofacitinib 5 mg b.i.d. (N = 58) [a]	Average tofacitinib 10 mg b.i.d. (N = 139) [a]	All tofacitinib (N = 197)	Average tofacitinib 5 mg b.i.d. (N = 1005) [a]	Average tofacitinib 10 mg b.i.d. (N = 2874) [a]	All tofacitinib (N = 3879)
Neutrophil count, ×1000/mm^3 [b]						
≥1.5-<2	2 (3.4) 2.25 (0.27-8.12)	4 (2.9) 0.88 (0.24-2.25)	6 (3.0) 1.10 (0.40-2.40)	71 (7.1) 3.03 (2.37-3.83)	178 (6.2) 1.58 (1.36-1.83)	249 (6.4) 1.83 (1.61-2.07)
≥0.5-<1.5	0 (0.0) 0.00 (0.00-4.06)	1 (0.7) 0.21 (0.01-1.19)	1 (0.5) 0.18 (0.00-1.00)	25 (2.5) 1.02 (0.66-1.50)	61 (2.1) 0.53 (0.40-0.68)	86 (2.2) 0.61 (0.49-0.76)
<0.5	0 (0.0) 0.00 (0.00-4.06)	0 (0.0) 0.00 (0.00-0.78)	0 (0.0) 0.00 (0.00-0.65)	0 (0.0) 0.00 (0.00-0.15)	0 (0.0) 0.00 (0.00-0.03)	0 (0.0) 0.0 (0.00-0.03)

Note: Confirmed values are based on two sequential measurements; N are patient numbers for both populations in the safety analysis set; the numbers of patients assessed for each endpoint may be lower than N; IRs are patients with events per 100 patient-years; for the Indian population, safety data were pooled from ORAL Scan, ORAL Solo, ORAL Start, and LTE study ORAL Sequel; ROW safety data were pooled from ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync, ORAL Start, ORAL Standard, ORAL Sequel, and A3921041.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.i.d., twice daily; CI, confidence interval; Hb, hemoglobin; IR, incidence rate; IU/L, international units per liter; LTE, long-term extension; NA, not available; ROW, rest of the world; TDD, total daily dose; ULN, upper limit of normal.

[a]The average TDD of tofacitinib for each patient was calculated as the sum of all doses received divided by the number of days of treatment over the entire study duration for each patient; average tofacitinib doses of 5 mg b.i.d. and 10 mg b.i.d. were defined as TDD <15 mg BID and TDD ≥15 mg b.i.d., respectively.

[b]Abnormality is defined as a count of <2×1000/mm^3.

there is an increased short-term risk of hospitalization for VTEs in patients initiating bDMARDs, compared with MTX,[32] although other studies have found no association between bDMARD use and risk of VTE[33]; therefore, the evidence for bDMARD use as a risk factor for VTE has not been confirmed.

Previously identified risk factors for ILD in patients with RA include older age, male gender, smoking status, disease activity, and high levels of serum rheumatoid factor (RF+) and antibodies against cyclic citrullinated peptide (anti-CCP+).[34,35] Also, in a recent post hoc analysis of data from the global tofacitinib clinical development program, ILD events were found to be associated with Asian ethnicity, smoking/history of smoking, and prior treatment with MTX, non-MTX csDMARDs, or TNFi.[36] In this analysis, rates of ILD were similar in Indian and ROW patients, despite higher rates of Asian ethnicity, overall RF+, and anti-CCP+ and prior non-MTX csDMARD use in the Indian population. This may be attributed to the fact that Indian patients were younger, and less likely to have smoked or have received prior treatment with MTX or TNFi, vs the ROW population.

IRs for laboratory abnormalities were generally similar in Indian and ROW patients, except for increased ALT >1 × ULN and lymphocyte counts ≥1.5-<2 × 1000/mm^3 and ≥0.5-<1.5 × 1000/mm^3, which did not translate into a difference in infection risk. Of note, no Indian patients receiving tofacitinib exhibited a lymphocyte count <0.5 × 1000/mm^3, which has previously been associated with increased risk of SIEs and an indication that the drug should be discontinued.[37]

These results are consistent with a prior post hoc analysis of tofacitinib efficacy and safety in 8 Asia-Pacific countries, which also found improvements in ACR20 response rates and change from baseline in HAQ-DI with tofacitinib, vs placebo, in Asia-Pacific and ROW populations at month 3.[15] The safety of tofacitinib was generally similar in both populations, but consistent with our findings, Asia-Pacific patients had higher rates of TB (IR = 0.6, 95% CI 0.4-0.9), compared with the global population (IR = 0.2, 95% CI 0.1-0.2). However, unlike the present analysis, this previous analysis found that, compared with the global population, Asia-Pacific patients had lower mortality rates (IR = 0.1, 95% CI 0.1-0.3 vs IR = 0.5, 95% CI 0.4-0.6 for the global population), and higher rates of discontinuations due to AEs (IR = 9.1, 95% CI 8.3-10.1 vs IR = 7.2, 95% CI 6.9-7.6 for the global population), SIEs (IR = 3.7, 95% CI 3.2-4.3 vs IR = 2.6, 95% CI 2.4-2.9 for the global population), and HZ (serious and non-serious; IR = 5.9, 95% CI 5.2-6.7 vs IR = 3.8 95% CI 3.5-4.1 for the global population), primarily driven by Japanese and Korean patients.

Previously, TB incidence following treatment with tofacitinib was evaluated in patients from countries at low, medium, and high risk of TB (IR = 0.02, 95% CI 0.003-0.15; IR = 0.08, 95% CI 0.03-0.21; and IR = 0.75, 95% CI 0.49-1.15, respectively).[38] The high-risk group included 1326 patients from 12 countries, including 194 patients from India. It was suggested that patients with latent TB infections could be treated with isoniazid during tofacitinib therapy. In the current analysis, Indian patients with untreated/inadequately treated latent TB infections received isoniazid for ≥1 month prior to enrollment, and no Indian patients developed TB during the analysis. Some patients from countries with a high risk of TB, but without latent TB at baseline, were subsequently positive in QuantiFERON-GOLD®™ testing post-baseline. However, none had active TB in follow-up chest radiograms. This highlights the importance of continuous monitoring of TB status during tofacitinib treatment, which is in line with annual testing for latent TB infection, as recommended in various guidelines for patients with a high risk of TB, especially those without latent TB prior to bDMARD treatment.[39-42]

Tuberculosis incidence with tofacitinib in Indian patients in this analysis was in line with that previously observed in country-specific data for patients with RA from countries with high TB incidence (Taiwan, Korea) receiving bDMARDs (IR = 0.00-2.56 per 100 patient-years).[43-46] TB incidence with tofacitinib in ROW patients was also consistent with that in global clinical trials of tofacitinib over 9.5 years (IR = 0.2, 95% CI 0.1-0.2).[10]

In India, advanced treatments for RA have not been used routinely, as drug costs are generally borne by the patient, which can be a challenge for those with a relatively low income.[47,48] Consequently, assessment of advanced therapies in Indian patients has been limited. One study evaluated the effects of etanercept or infliximab in patients with an inadequate response to csDMARDs, and the effects of rituximab, abatacept, or tocilizumab in Indian patients who had previously failed TNFi. Significant reductions from baseline in disease activity (as measured by DAS28-4[ESR] scores) were observed with bDMARDs in both cohorts; however, rates of DAS28-4(ESR)-defined remission and low disease activity could not be determined, due to the small study population.[47]

This analysis had a number of limitations and data should therefore be interpreted with caution. This was a post hoc analysis, which used data pooled from studies with different study designs and methodologies, and different study populations. There were differences in the studies included for the Indian and ROW populations, as not all Phase 3/LTE studies included patients from India. In the safety analysis, more Indian patients were from the ORAL Start study and were MTX-naïve, compared with ROW patients, and all Indian patients were bDMARD-naïve, whereas the ROW population included TNFi-inadequate responders from ORAL Step. These differences may partially explain the comparatively lower proportion of Indian patients with AEs and SAEs, compared with the ROW population, as there is evidence that the risk of some AEs is increased by the use of RA treatments,[49-52] and the risk of some AEs has also been shown to differ in csDMARD-IR vs bDMARD-IR patients receiving tofacitinib.[53] However, conversely, rates of AESI were similar in both populations, despite Indian patients being younger, having no prior bDMARD experience, shorter disease duration, and higher baseline disease activity, compared with the ROW population. It is also possible that there were differences in undertreatment or delayed treatment between the two populations, which may confound interpretation of these results. It is also important to note that the sample size and patient exposure in the Indian population were smaller than in the ROW population, and 95% CIs were wide, limiting our ability to discern differences (numerical or otherwise) between populations. Also, all analyses were descriptive in nature, only general trends are described, and no formal statistical analyses were carried out.

In conclusion, the efficacy of tofacitinib in Indian patients with RA was similar to that in ROW patients. These results help provide insight into the benefit: risk profile of tofacitinib in Indian patients with RA.

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CONFLICT OF INTEREST

A. Chopra, V. Shobha, S. Chandrashekara, R. Sharma, U.R. Rao, S. Wagh, and J.K. Kadel were paid investigators for Pfizer Inc; A.V. Thorat, C. Adhav, P. Santos Estrella, W. Yu, K. Kwok, and A. Wouters are employees and stockholders of Pfizer Inc; S.C.M. Veeravalli and S. Pandya have declared no conflicts.

AUTHOR CONTRIBUTIONS

A. Chopra, A.V. Thorat, P. Santos Estrella, K. Kwok, and A. Wouters were involved in conception and design of the analysis; K. Kwok, A. Wouters, and A.V. Thorat were involved in data analysis; all authors were involved in data interpretation, and in development and revision of the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

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 (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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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