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# Tofacitinib 5 mg Twice Daily in Patients with Rheumatoid Arthritis and Inadequate Response to Disease-Modifying Antirheumatic Drugs

## *A Comprehensive Review of Phase 3 Efficacy and Safety*

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**Background:** Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We performed a comprehensive review of phase 3 studies of tofacitinib 5 mg twice daily (BID) (approved dose in many countries) in patients with moderate to severe RA and inadequate response to prior disease-modifying antirheumatic drugs.

**Methods:** A search of PubMed and ClinicalTrials.gov identified 5 studies: ORAL Solo (NCT00814307), ORAL Sync (NCT00856544), ORAL Standard (included adalimumab 40 mg once every 2 weeks; NCT00853385), ORAL Scan (NCT00847613), and ORAL Step (NCT00960440). Efficacy and safety data for tofacitinib 5 mg BID, placebo, and adalimumab were analyzed.

**Results:** Across the 5 studies, 1216 patients received tofacitinib 5 mg BID, 681 received placebo, and 204 received adalimumab. At month 3, tofacitinib demonstrated significantly higher 20%, 50%, and 70% improvement in American College of Rheumatology response criteria (ACR20, ACR50, and ACR70, respectively) response rates, greater improvement in Health Assessment Questionnaire-Disability Index, and a higher proportion of

Disease Activity Score-defined remission than placebo. Frequencies of adverse events (AEs), serious AEs, and discontinuations due to AEs were similar for tofacitinib and placebo at month 3; serious infection events were more frequent for tofacitinib. In ORAL Standard, although not powered for formal comparisons, tofacitinib and adalimumab had numerically similar efficacy and AEs; serious AEs and serious infection events were more frequent with tofacitinib.

**Conclusions:** Tofacitinib 5 mg BID reduced RA signs and symptoms and improved physical function versus placebo in patients with inadequate response to prior disease-modifying antirheumatic drugs. Tofacitinib 5 mg BID had a consistent, manageable safety profile across studies, with no new safety signals identified.

**Key Words:** efficacy, phase 3, rheumatoid arthritis, safety, tofacitinib

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Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease associated with considerable morbidity and diminished quality of life and characterized by persistent synovitis, systemic inflammation, and ultimately joint destruction.<sup>1–4</sup> Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), are recommended as first-line therapy for RA and are often followed by biologic DMARDs (bDMARDs), such as tumor necrosis factor inhibitors (TNFi), for patients who have an inadequate response (IR).<sup>5,6</sup> Earlier and more aggressive use of csDMARDs and the introduction of bDMARDs have improved outcomes for patients.<sup>4</sup> However, existing treatment regimens are not effective in all patients, and bDMARDs that require parenteral administration are not universally available.<sup>7</sup> In addition, only between 24% and 58% of patients achieve 20% improvement in American College of Rheumatology response criteria (ACR20) after 1 year of treatment.<sup>8–11</sup> Despite the variety of targeted bDMARDs available (e.g., TNFi, interleukin inhibitors, and T- and B-cell inhibitors), some patients with active, uncontrolled disease are unable to receive these treatments, additional patients lose clinical response, and some are subject to unacceptable risks.<sup>8–10,12</sup> Therefore, a need remains for RA therapies with alternative mechanisms of action to provide patients with additional therapeutic options to manage this chronic and progressive condition.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. The JAK family of kinases mediates intracellular signal transduction of cytokines involved in immune regulation and has been linked to regulation of the intensity and duration of inflammatory responses, implicating it in chronic inflammatory diseases, including RA.<sup>13,14</sup> Tofacitinib preferentially inhibits signaling via JAK3 and JAK1 with functional selectivity over JAK2.<sup>15,16</sup> JAK inhibition blocks the signaling pathways involved in lymphocyte activation, proliferation, and function and may thus modulate the immune response, including reducing inflammation.<sup>15,17</sup> Phase 2, dose-ranging, randomized controlled trials

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provided sufficient evidence for phase 3 studies of tofacitinib in patients with RA administered as monotherapy or in combination with MTX.<sup>18–22</sup> Long-term extension (LTE) studies (1 complete and 1 ongoing) to evaluate tofacitinib safety and efficacy over longer periods have been reported for patients who completed phase 2 and 3 studies.<sup>23,24</sup>

While the phase 3 studies examined 2 separate doses of tofacitinib—5 and 10 mg twice daily (BID)—based on the results of the phase 3 program, tofacitinib has been approved in many countries at a 5-mg BID dose for patients with active RA and an IR or intolerance to prior DMARD treatment.<sup>25–30</sup> We present a review of tofacitinib 5 mg BID phase 3 data in patients with RA and prior IR to DMARDs (DMARD-IR), in order to provide a comprehensive summary of the efficacy and safety of the widely approved dose in the phase 3 program and to allow comparison of results across the pivotal phase 3 registration studies, including patients with IR to csDMARDs and bDMARDs.

## METHODS

### Search Strategy

In order to identify all relevant articles to include in this review, a search was conducted in the PubMed and ClinicalTrials.gov databases to identify primary reports of phase 3 randomized controlled trial data for tofacitinib 5 mg BID in patients with active RA and DMARD-IR. We used the search string “tofacitinib AND phase III AND rheumatoid arthritis” to interrogate both databases and identified 38 articles in PubMed and 12 studies in ClinicalTrials.gov. Search results were then assessed for eligibility based on the following inclusion criteria: phase 3 study, patients received tofacitinib 5 mg BID, patients had active RA, patients had previously received DMARDs and were DMARD-IR, and the study was completed and results were available. In total, 5 studies and corresponding articles were identified that matched all of these criteria: ORAL Solo (NCT00814307, A3921045)<sup>28</sup>; ORAL Sync (NCT00856544, A3921046)<sup>25</sup>; ORAL Standard (NCT00853385, A3921064)<sup>26</sup>; ORAL Scan (NCT00847613, A3921044)<sup>30</sup>; and ORAL Step (NCT00960440, A3921032).<sup>29</sup>

Further information about the design of the 5 studies analyzed is presented in Table 1. Data are reviewed from patients who were randomly assigned to receive tofacitinib 5 mg BID, placebo advanced to tofacitinib 5 mg BID, or adalimumab 40 mg once every 2 weeks (Q2W; ORAL Standard only). Placebo-treated patients advanced to tofacitinib 5 mg BID at month 3 or month 6, depending on disease activity and according to randomization. The 5 studies also included tofacitinib 10 mg BID and placebo advanced to tofacitinib 10 mg BID treatment arms, which are

not included in this review. Patients received stable background DMARDs in all studies, except ORAL Solo.

We also identified 5 pooled analyses of safety outcomes covering the tofacitinib clinical development program, which included data from the phase 3 trials.<sup>23,31–35</sup> We also requested and received further information regarding laboratory parameters for each study, as there was wide variation in reporting within the identified primary and safety articles. These reports supplemented our safety analyses of tofacitinib 5 mg BID.

### End Points Evaluated

The phase 3 studies identified in the literature search were reviewed, and data for efficacy and safety end points were extracted. Co-primary end points in all 5 studies were ACR20 rate, least-squares (LS) mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI), and Disease Activity Score (DAS)-defined remission (DAS28-4 erythrocyte sedimentation rate [ESR] <2.6). Radiographic progression, assessed by LS mean change from baseline in modified Total Sharp Score (mTSS), was also a co-primary end point in ORAL Scan. Secondary study end points included ACR50 and ACR70 rates and the proportion of patients with no radiographic progression (change from baseline in mTSS ≤0.5; ORAL Scan only).

Co-primary end points were measured at month 3 or month 6 and were assessed using a step-down procedure: statistical significance could be claimed only if the prior end point in the sequence met significance requirements. For this review, we primarily evaluated end points at month 3, because this was the most consistent time point across the studies, that is, before placebo-treated patients advanced, so all patients had received their assigned study medication for 3 months. Missing values for binary efficacy variables (e.g., ACR response rates and DAS28-4 [ESR] <2.6) were imputed using nonresponder imputation. The normal approximation was used to test the treatment difference in proportions. Missing values for HAQ-DI were handled using a linear mixed-effects model with treatment effect assessed from the same model. For mTSS, missing values were imputed using linear extrapolation.

In all 5 studies, safety end points included adverse event (AE) reports, discontinuations due to AEs, serious AEs (SAEs), and clinical laboratory abnormalities. For this review, the most frequent AEs/SAEs were determined by first identifying the AEs/SAEs with the 3 highest percentage values for each study; those AEs/SAEs occurring in 2 or more studies were then identified as the most frequent. In each study, AEs of special interest were analyzed in further detail. These related to safety signals associated with RA treatment and those identified during the tofacitinib clinical development program, including serious infection events

**TABLE 1.** Study Design Information for the 5 Phase 3 Studies

	ORAL Solo	ORAL Sync	ORAL Standard	ORAL Scan	ORAL Step
Study duration	6 mo	12 mo	12 mo	24 mo	6 mo
Previous IR	DMARD	DMARD	Methotrexate	Methotrexate	TNFi
Study treatments <sup>a</sup>	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo Adalimumab 40 mg Q2W	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo
Background medications	None	csDMARDs	Methotrexate	Methotrexate	Methotrexate

<sup>a</sup>All placebo-treated patients advanced to tofacitinib 5 or 10 mg BID after month 3 or 6, depending on disease activity and according to randomization. cs indicates conventional synthetic; DMARD, disease-modifying antirheumatic drug.

(SIEs), opportunistic infections (OIs), malignancies, lymphomas, lymphocyte and neutrophil levels, and changes in levels of liver transaminases, hemoglobin, lipids, and serum creatinine.

## RESULTS

### Patients

Across the 5 studies, 1216 patients received tofacitinib 5 mg BID, 681 received placebo, and 204 received adalimumab 40 mg Q2W. Patient selection criteria were similar across the studies, with all 5 studies enrolling patients 18 years or older, with active RA based on the ACR 1987 Revised Criteria, and active disease defined by at least 4 (ORAL Sync) or at least 6 (all other studies) tender/painful joints, at least 4 (ORAL Sync) or at least 6 (all other studies) swollen joints, and ESR greater than 28 mm/h or C-reactive protein greater than 7 mg/L. Additional criteria that applied to ORAL Scan were evidence of 3 or more distinct joint erosions or, if radiographic evidence of joint erosions was unavailable, rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP) positive. Requirements for prior DMARD use varied across studies, with ORAL Scan and ORAL Standard enrolling MTX-IR patients, ORAL Sync and ORAL Solo enrolling csDMARD-IR or bDMARD-IR patients, and ORAL Step enrolling TNFi-IR patients. Patient exclusion criteria relating to AEs and laboratory parameters were similar across studies.

Baseline demographics and disease characteristics were generally well balanced between the treatment arms of individual studies and similar across all 5 studies (Table 2); the only exception was longer disease duration in ORAL Step (TNFi-IR) than the other 4 studies (DMARD-IR, MTX-IR) (Table 2).

### Efficacy

Across the phase 3 studies at month 3, ACR20 rates were significantly higher with tofacitinib 5 mg BID versus placebo, either as monotherapy or with background DMARDs (Table 3, Fig. 1). Significantly higher ACR20 rates for tofacitinib 5 mg BID versus placebo were observed at the first evaluable time point in each study (week 2 or month 1; Fig. 1). The ACR50 and ACR70 rates followed similar patterns (Table 3). The ACR20 rates were sustained over the remaining study periods for the tofacitinib 5 mg BID group, and similar ACR20 rates were observed after switching for patients who advanced to tofacitinib after 3 or 6 months on placebo (Fig. 1).

The LS mean increases from baseline in mTSS (measured in ORAL Scan only) were numerically greater for placebo-treated patients compared with those receiving tofacitinib 5 mg BID at month 6, but this difference was not statistically significant (Table 3). Post hoc analyses of the interim study data demonstrated that patients with prognostic factors predictive of greater progression of joint damage (anti-CCP positivity, DAS28-4 [ESR] >5.1, anti-CCP and/or rheumatoid factor positivity with erosion score  $\geq 3$ , and baseline total mTSS greater than the baseline median) had more pronounced effects with tofacitinib 5 mg BID versus placebo.<sup>30</sup> The proportion of patients with no radiographic progression at month 6 was significantly greater in the tofacitinib 5 mg BID group (88.8%) compared with the placebo group (77.7%;  $p \leq 0.01$ ).

Greater LS mean improvements from baseline in HAQ-DI were observed across the phase 3 studies at month 3 for patients treated with tofacitinib 5 mg BID than placebo (Table 3; Fig. 2). These improvements were significant for tofacitinib versus placebo, except in ORAL Scan, where significance was not declared because of the step-down procedure. Improvements were observed for tofacitinib 5 mg BID administered as monotherapy or with

background csDMARDs. Patients advancing to tofacitinib 5 mg BID after 3 or 6 months on placebo reported HAQ-DI improvements following advancement (Fig. 2). Observed HAQ-DI improvements from baseline with tofacitinib 5 mg BID were sustained over the remaining study periods (Fig. 2).

Across the 5 phase 3 studies, more patients receiving tofacitinib 5 mg BID achieved DAS-defined remission (DAS28-4 [ESR] <2.6) at month 3 compared with placebo-treated patients (Table 3). These differences were significant in ORAL Sync, ORAL Standard, and ORAL Step; because of the step-down procedure, significance was not declared in ORAL Scan.

In ORAL Standard, efficacy responses were numerically similar for patients receiving tofacitinib 5 mg BID or adalimumab 40 mg Q2W, although ORAL Standard was not designed for non-inferiority or superiority comparisons between tofacitinib and adalimumab (Figs. 1 and 2, Table 3).

### Safety

As expected for active treatment arms, frequencies of AEs and SAEs were slightly higher with tofacitinib compared with placebo groups across all of the phase 3 studies between baseline and month 3 (patient-years of exposure for tofacitinib 5 mg BID vs. placebo for ORAL Solo, ORAL Sync, ORAL Standard, ORAL Scan, and ORAL Step: 30.1 vs. 15.0, 77.8 vs. 39.3, 49.0 vs. 26.5, 154.5 vs. 77.0, 16.5 vs. 16.4; Fig. 3). In total, 51.6% and 53.0% of patients receiving tofacitinib 5 mg BID and placebo, respectively, had AEs in the first 3 months. During this period, the most frequent AEs were diarrhea (2.2%–6.0%), headache (1.3%–5.6%), nasopharyngitis (1.6%–5.9%), and upper respiratory tract infection (2.8%–10.5%) for patients receiving tofacitinib 5 mg BID; and arthralgia (0.0%–3.8%), cough (0.0%–3.8%), peripheral edema (0.0%–3.8%), and upper respiratory tract infection (0.9%–4.9%) for placebo-treated patients. There were no frequent SAEs (all  $\leq 1\%$ ) reported in either the tofacitinib 5 mg BID or placebo groups; SAEs were experienced by 2.9% of tofacitinib-treated patients and 4.1% of placebo-treated patients. During the first 3 months of treatment, 4.2% and 3.2% of tofacitinib- and placebo-treated patients discontinued because of AEs, respectively (Fig. 3). In ORAL Standard, tofacitinib- and adalimumab-treated patients reported generally similar AE rates: 52.0% for tofacitinib and 51.5% for adalimumab (patient-years of exposure to month 3 for tofacitinib 5 mg BID vs. adalimumab 40 mg Q2W: 49.0 vs. 49.8; Fig. 3). Although there were few SAEs or discontinuations due to AEs with both tofacitinib (5.9% and 6.9%, respectively) and adalimumab (2.5% and 4.9%, respectively), SAEs and discontinuations due to AEs were numerically higher with tofacitinib than adalimumab.

Overall, the most frequently reported infections for tofacitinib 5 mg BID and placebo across the full reported study periods (6 or 12 months) of the phase 3 studies were bronchitis ( $n = 14$  and  $n = 10$ , respectively), herpes zoster (HZ;  $n = 5$  and  $n = 2$ , respectively), influenza ( $n = 8$  and  $n = 5$ , respectively), nasopharyngitis ( $n = 47$  and  $n = 19$ , respectively), upper respiratory tract infection ( $n = 53$  and  $n = 23$ , respectively), and urinary tract infection ( $n = 25$  and  $n = 12$ , respectively) (patient-years of exposure for tofacitinib 5 mg BID vs. placebo: 1311.5 vs. 696.5).<sup>34</sup> As expected for active treatment, SIEs were numerically more frequent in tofacitinib groups than in placebo groups; 29 patients receiving tofacitinib 5 mg BID and 3 placebo-treated patients reported SIEs.<sup>34</sup> A total of 4 OIs were reported with tofacitinib 5 mg BID: 1 case each of disseminated HZ and *Pneumocystis jirovecii* pneumonia and 2 cases of esophageal candidiasis. Any patients with evidence of active, latent, or inadequately treated tuberculosis (TB) at screening were excluded from the studies, and

TABLE 2. Baseline Demographics and Patient Characteristics across Phase 3 Studies

Parameter	ORAL Solo		ORAL Sync		ORAL Standard		ORAL Scan		ORAL Step		
	Tofacitinib 5 mg BID (n = 243)	Placebo (n = 122)	Tofacitinib 5 mg BID (n = 315)	Placebo (n = 159)	Tofacitinib 5 mg BID (n = 204)	Placebo (n = 108)	Adalimumab 40 mg Q2W (n = 204)	Tofacitinib 5 mg BID (n = 321)	Placebo (n = 160)	Tofacitinib 5 mg BID (n = 133)	Placebo (n = 132)
Population											
Female, n (%)	207 (85.2)	105 (86.1)	264 (83.8)	123 (77.4)	174 (85.3)	82 (75.9)	162 (79.4)	269 (83.8)	137 (85.6)	113 (85.0)	106 (80.3)
White, n (%)	153 (63.0)	88 (72.1)	173 (54.9)	92 (57.9)	151 (74.0)	75 (69.4)	148 (72.5)	152 (47.4)	72 (45.0)	108 (81.2)	112 (84.8)
Mean (SD) age, y	52.2 (11.5)	49.7 (12.4)	52.7 (11.7)	52.1 (11.0)	53.0 (11.9)	53.8 (13.7)	52.5 (11.7)	53.7 (11.6)	52.6 (11.6)	55.4 (11.5)	54.4 (11.3)
Mean (range) disease duration, y	8.0 (0.2–42.3)	7.7 (0.2–28.0)	8.1 (0.2–39.9)	9.9 (0.3–49.0)	7.6 (0.3–39.0)	8.0 (0.3–49.4)	8.1 (0.2–36.3)	8.9 (0.3–43.0)	9.2 (0.4–43.5)	13.0 (1.2–55.0)	11.3 (0.4–47.0)
Mean (SD) tender joint count	29.0 (15.0)	29.0 (16.0)	25.0 (15.3)	25.0 (15.2) <sup>a</sup>	28.0 (15.0) <sup>a</sup>	27.0 (14.3) <sup>a</sup>	27.0 (15.3) <sup>a</sup>	24.0 (14.0)	23.0 (13.1) <sup>a</sup>	28.0 (18.3)	28.0 (16.7)
Mean (SD) swollen joint count	16.0 (8.6)	17.0 (10.7)	14.0 (10.3)	14.0 (9.1) <sup>a</sup>	17.0 (8.8) <sup>a</sup>	17.0 (8.8) <sup>a</sup>	16.0 (8.7) <sup>a</sup>	14.0 (8.2)	14.0 (8.4) <sup>a</sup>	16.0 (10.1)	17.0 (10.7)
Mean (SD) mTSS	—	—	—	—	—	—	—	31.1 (47.7)	32.6 (41.8)	—	—
Mean (SD) HAQ-DI	1.5 (0.7)	1.5 (0.7)	1.4 (0.7)	1.4 (0.7) <sup>a</sup>	1.5 (0.6) <sup>a</sup>	1.4 (0.7) <sup>a</sup>	1.5 (0.7) <sup>a</sup>	1.4 (0.7)	1.3 (0.7) <sup>a</sup>	1.6 (0.7)	1.6 (0.7)
Mean (SD) DAS28-4 (ESR)	6.7 (0.9) <sup>a</sup>	6.6 (0.9) <sup>a</sup>	6.3 (1.0) <sup>a</sup>	6.3 (0.9) <sup>a</sup>	6.6 (0.9) <sup>a</sup>	6.5 (0.9) <sup>a</sup>	6.4 (0.9) <sup>a</sup>	6.3 (1.0) <sup>a</sup>	6.3 (1.0) <sup>a</sup>	6.5 (1.0) <sup>a</sup>	6.5 (1.0) <sup>a</sup>
Mean (SD) DAS28-3 (CRP)	5.7 (0.9)	5.6 (0.9)	5.2 (0.9)	5.2 (0.9) <sup>a</sup>	5.4 (0.9) <sup>a</sup>	5.4 (0.9) <sup>a</sup>	5.3 (0.9) <sup>a</sup>	5.2 (0.9)	5.16 (0.9) <sup>a</sup>	5.4 (1.0)	5.4 (1.0)

<sup>a</sup>N numbers were slightly less than the N number stated based on data collection and availability. CRP indicates C-reactive protein; DMARD, disease-modifying antirheumatic drug; SD, standard deviation.

**TABLE 3. Efficacy Outcomes across Phase 3 Studies**

Outcome	ORAL Solo		ORAL Sync		ORAL Standard		ORAL Scan		ORAL Step		
	Tofacitinib 5 mg BID (n = 241)	Placebo (n = 120)	Tofacitinib 5 mg BID (n = 311)	Placebo (n = 157)	Tofacitinib 5 mg BID (n = 196)	Placebo (n = 106)	Adalimumab 40 mg Q2W (n = 199)	Tofacitinib 5 mg BID (n = 309)	Placebo (n = 154)	Tofacitinib 5 mg BID (n = 132)	Placebo (n = 131)
ACR20, n (%)	144 (59.8) <sup>ab</sup>	32 (26.7)	175 (56.3) <sup>b</sup>	43 (27.4)	119 (60.7) <sup>b</sup>	28 (26.4)	112 (56.3)	174 (56.3) <sup>b</sup>	42 (27.3)	55 (41.7) <sup>ac</sup>	32 (24.4)
ACR50, n (%)	75 (31.1) <sup>b</sup>	15 (12.5)	85 (27.3) <sup>b</sup>	15 (9.6)	67 (34.2) <sup>b</sup>	7 (6.6)	47 (23.6)	89 (28.8) <sup>b</sup>	12 (7.8)	35 (26.5) <sup>b</sup>	11 (8.4)
ACR70, n (%)	37 (15.4) <sup>c</sup>	7 (5.8)	26 (8.4) <sup>d</sup>	3 (1.9)	24 (12.2) <sup>d</sup>	2 (1.9)	17 (8.5)	33 (10.7) <sup>d</sup>	4 (2.6)	18 (13.6) <sup>d</sup>	2 (1.5)
LS mean (SE) change from baseline at month 6 in mTSS	—	—	—	—	—	—	—	0.12 (0.12) <sup>e</sup>	0.47 (0.16)	—	—
LS mean (SE) change from baseline in HAQ-DI	—	—	—	—	—	—	—	—	—	—	—
DAS28-4 (ESR) <2.6, n (%)	13 (5.6) <sup>ae</sup>	5 (4.4) <sup>e</sup>	26 (10.0) <sup>be</sup>	1 (0.7) <sup>e</sup>	9 (5.1) <sup>ce</sup>	1 (1.1) <sup>e</sup>	7 (3.9) <sup>e</sup>	14 (5.3) <sup>e</sup>	2 (1.6) <sup>e</sup>	8 (6.7) <sup>ac,e</sup>	2 (1.7) <sup>e</sup>

Efficacy end points are measured at month 3, unless otherwise indicated; DAS28-4 (ESR) <2.6 is DAS-defined remission. Because of the step-down method, significance was not declared for mTSS, HAQ-DI, or DAS28-4 (ESR) in ORAL Scan. FAS, NRI for ACR and DAS end points; FAS, longitudinal model for HAQ-DI.

<sup>a</sup>Primary end point of the study.

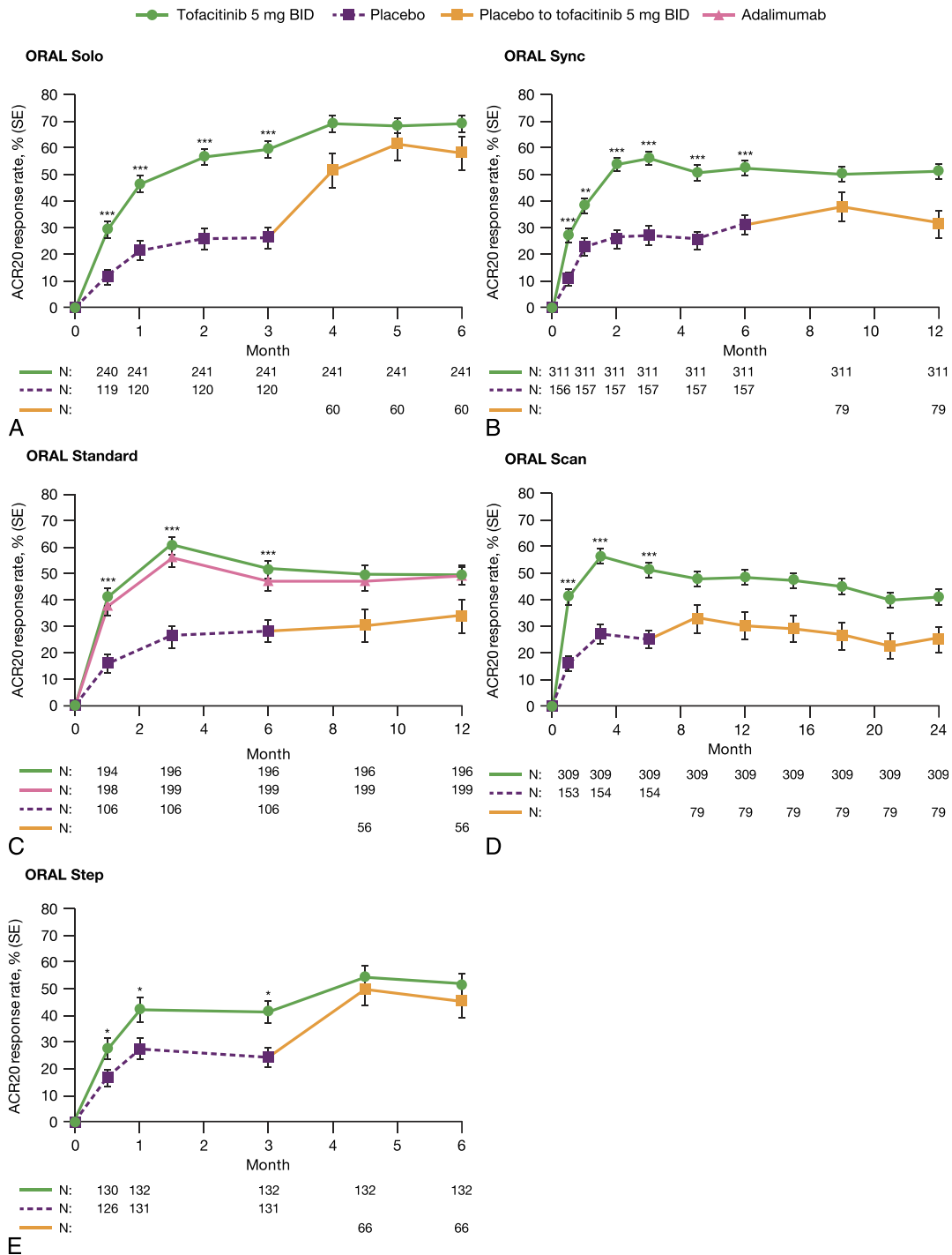
<sup>b</sup>*p* < 0.0001 versus placebo.

<sup>c</sup>*p* < 0.05.

<sup>d</sup>*p* < 0.001.

<sup>e</sup>N numbers were slightly less than the N number stated based on data collection and availability.

ACR20/50/70 indicates proportion of patients achieving ≥20%, ≥50%, and ≥70% improvement in American College of Rheumatology criteria; DAS, disease activity score; FAS, full analysis set; LS, least squares; NRI, non-responder imputation; SE, standard error.

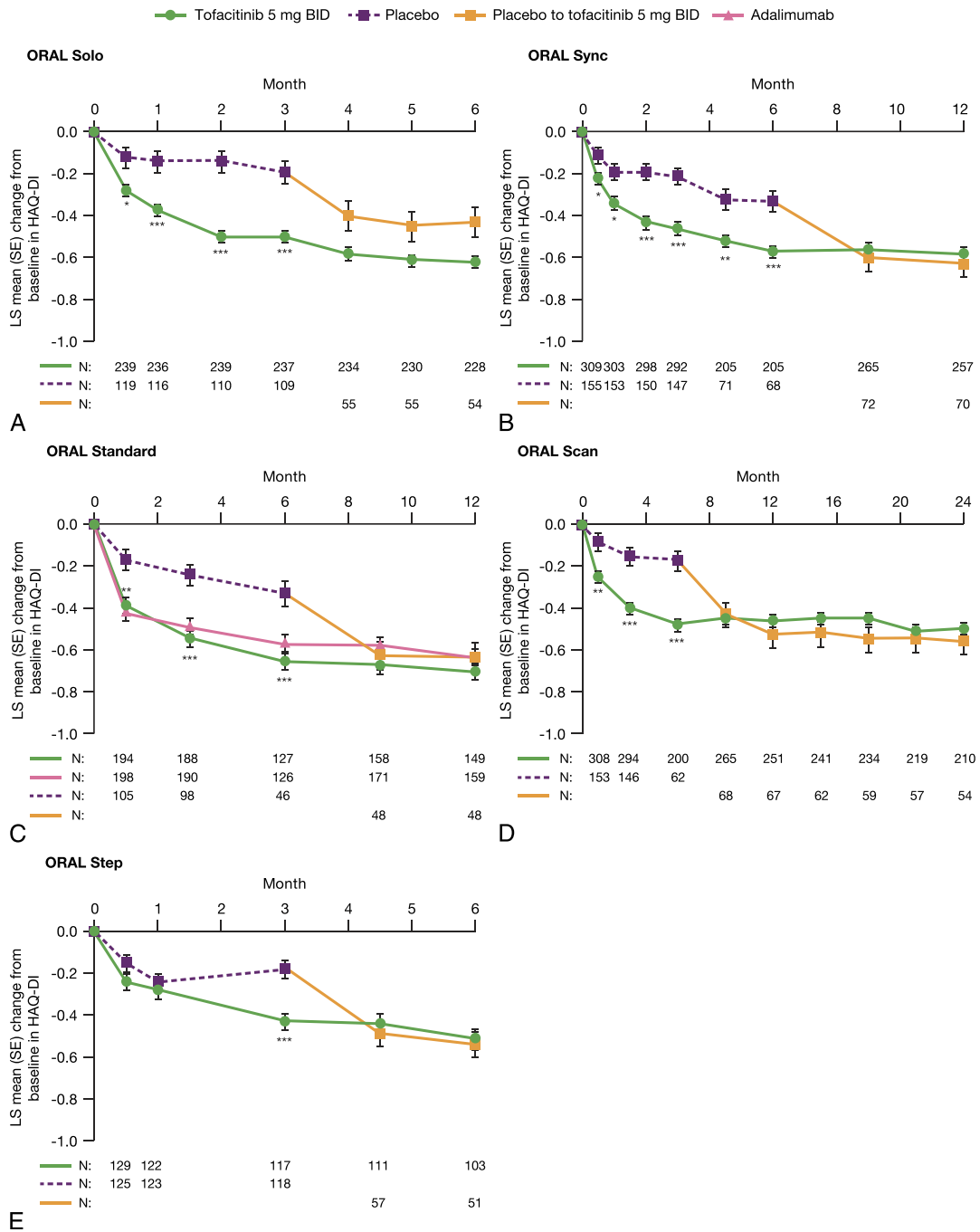


**FIGURE 1.** The ACR20 response rates (% [SE]) over time in the phase 3 studies (FAS, NRI). \* $p < 0.05$ , \*\* $p < 0.001$ , \*\*\* $p < 0.0001$  versus placebo. The ACR20 response rate at month 3 was a primary end point in the ORAL Solo and ORAL Step studies, and the ACR20 response rate at month 6 was a primary end point in the ORAL Sync, ORAL Scan, and ORAL Standard studies. ACR20 indicates  $\geq 20\%$  improvement in American College of Rheumatology criteria; FAS, full analysis set; N, number of patients included in analysis; NRI, non-responder imputation; SE, standard error. Color online-figure is available at <http://www.jclinrheum.com>.

no cases of TB were reported in patients receiving tofacitinib 5 mg BID or placebo during any of the phase 3 studies.<sup>36</sup>

Malignancies (excluding nonmelanoma skin cancer [NMSC]) were reported in 8 patients in the tofacitinib 5 mg BID groups across the full reported study periods (6 or 12 months) of the phase 3 studies (incidence rate, 0.55 [95% confidence interval,

0.27–1.09]; patient-years of exposure for tofacitinib 5 mg BID vs. placebo: 1311.5 vs. 696.5).<sup>31</sup> Six patients in the tofacitinib 5 mg BID groups reported NMSC (incidence rate, 0.41 [95% confidence interval, 0.19–0.92]).<sup>31</sup> Eight patients receiving tofacitinib 5 mg BID had more than 1 malignancy (1 patient had esophageal carcinoma and colon carcinoma, 1 patient had prostate cancer and

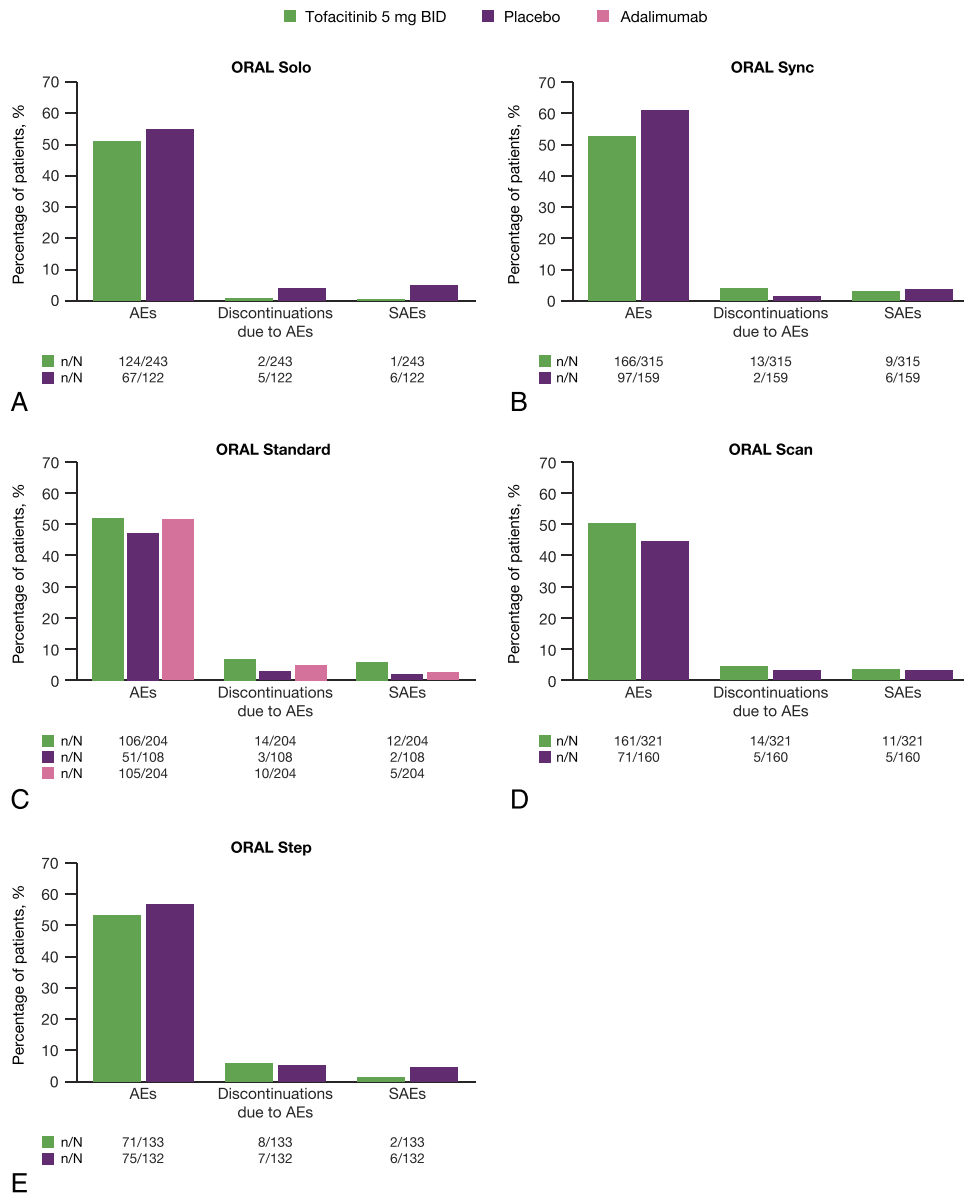


**FIGURE 2.** Least-squares mean (SE) change from baseline in HAQ-DI over time in the phase 3 studies (FAS, longitudinal model). \* $p < 0.05$ , \*\* $p < 0.001$ , \*\*\* $p < 0.0001$  versus placebo. Least-squares mean change from baseline at month 3 was the primary end point across studies. Because of the step-down method, significance was not declared in ORAL Scan. FAS indicates full analysis set; HAQ-DI, Health Assessment Questionnaire / Disability Index; LS, least squares; N, number of patients included in analysis; SE, standard error. Color online-figure is available at <http://www.jclinrheum.com>.

basal cell carcinoma, 3 patients had 2 basal cell carcinomas, 2 patients had 2 squamous cell carcinomas, and 1 patient had squamous cell carcinoma and basal cell carcinoma).<sup>31</sup> Two patients receiving tofacitinib 5 mg BID were reported to have lymphoma, and 2 placebo-treated patients reported NMSC.<sup>31</sup> In ORAL Standard, malignancy (excluding NMSC) was reported in 1 patient

(lung cancer) receiving adalimumab 40 mg Q2W (199 patient-years of exposure).

Four cardiovascular events were reported across the full reported study periods (6 or 12 months) for patients receiving tofacitinib 5 mg BID (1 each of transient ischemic attack [ORAL Sync], cerebrovascular accident [ORAL Sync], angina pectoris



**FIGURE 3.** Safety outcomes at month 3 across the phase 3 studies. n, number of patients with event; N, number of patients included in analysis; SAE, serious adverse event. Color online-figure is available at <http://www.jclinrheum.com>.

[ORAL Scan], coronary artery disease [ORAL Scan]) and none in placebo-treated patients (patient-years of exposure for tofacitinib 5 mg BID vs. placebo: 1311.5 vs. 696.5). One patient receiving adalimumab 40 mg Q2W in ORAL Standard reported 3 cardiovascular events (myocardial infarction, cardiac arrest, myocardial ischemia; 199 patient-years of exposure).

For patients receiving tofacitinib 5 mg BID, 5 deaths occurred up to 30 days from the last dose of study drug; 2 further deaths were reported after this time (1311.5 patient-years of exposure).<sup>34</sup> One death was considered treatment related (pneumonia n = 1), 4 were considered possibly treatment related (*P. jirovecii* n = 1, septic syndrome n = 1, acute respiratory distress and pneumonia n = 1, metastatic lung cancer n = 1), and 2 were considered unrelated to study treatment (traumatic brain injury n = 1, viral infection n = 1).<sup>34</sup> One death was reported in the placebo groups (696.5 patient-years of exposure).

Across the 5 phase 3 studies, decreases from baseline in neutrophil and lymphocyte counts and increases in hemoglobin and lipid levels, relative to placebo, were observed by month 3 with tofacitinib 5 mg BID (297.23 patient-years of exposure) and stabilized thereafter. Dose-dependent decreases in neutrophil counts were seen with tofacitinib and adalimumab, with similar magnitudes of change, in ORAL Standard and stabilized for all treatment groups thereafter. Neutropenia was more frequently reported in tofacitinib groups than in placebo groups, although no life-threatening cases of neutropenia were reported, and no SIEs were associated with neutropenia. The frequency of occurrence of lymphopenia was similar between tofacitinib- and placebo-treated patients.<sup>34</sup> One placebo-treated patient withdrew from ORAL Step because of decreased hemoglobin levels. Four patients receiving tofacitinib 5 mg BID had confirmed greater than 50% increase in serum creatinine from baseline. One patient



in the placebo to tofacitinib 5 mg BID group discontinued because of this, with levels subsequently stabilizing.

## DISCUSSION

A large clinical program comprising phase 3 data from more than 4000 patients<sup>23</sup> resulted in the approval of tofacitinib for the treatment of RA in many countries at a 5-mg BID dose. In 5 phase 3 studies enrolling patients with various treatment histories (Table 1), tofacitinib 5 mg BID rapidly reduced the signs and symptoms of RA and improved physical function when administered as monotherapy or with background csDMARDs. Tofacitinib 5 mg BID provided clinically meaningful improvements, as well as clinical and functional superiority to placebo, in patients with prior DMARD-IR. The variety of treatment backgrounds in these phase 3 studies (i.e., MTX, csDMARD, TNF-bDMARDs, and non-TNF-bDMARDs) demonstrated that tofacitinib could be effective for patients with a range of treatment histories in clinical practice. Across the 5 phase 3 studies, patients who advanced to tofacitinib 5 mg BID after 3 or 6 months on placebo had improvements in efficacy following the switch. These phase 3 results are consistent with efficacy results from phase 2 trials of tofacitinib 5 mg BID in DMARD-IR patients.<sup>18–20,22</sup> Tofacitinib 5 mg BID had numerically similar efficacy results to adalimumab with MTX in ORAL Standard. The objectives of the ORAL Standard study were to compare the efficacy of tofacitinib with placebo and to compare adalimumab with placebo. It was not powered to detect noninferiority or superiority between tofacitinib and adalimumab, but the inclusion of this active control group allowed estimates of the relative efficacy of tofacitinib.

Identified safety events up to month 3 (patient-years of exposure for tofacitinib 5 mg BID vs. placebo: 297.25 vs. 167) were consistent across the 5 studies and generally consistent with phase 2<sup>18–20,22</sup> and LTE<sup>23</sup> studies. The proportions of patients reporting AEs, SAEs, SIEs, and discontinuing due to AEs were numerically higher for tofacitinib than adalimumab in ORAL Standard.

In the phase 3 studies, SIEs were generally more frequent with tofacitinib 5 mg BID than placebo (1311.5 vs. 696.5 patient-years of exposure, respectively), and rates were similar to those in phase 2 studies.<sup>18–20,22</sup> A pooled analysis of infections across phase 2, phase 3, and LTE studies of tofacitinib found the overall SIE rate with tofacitinib (5 and 10 mg BID) to be 3.1 events per 100 patient-years.<sup>34</sup> The SIE rate was 3.2 events per 100 patient-years for tofacitinib 5 mg BID versus 1.5 events per 100 patient-years for placebo from pooled phase 3 study data.<sup>34</sup> Serious infection events have been reported at similar rates (1.5–9.2 events per 100 patient-years) in safety analyses of DMARDs,<sup>37–42</sup> TNFi observational studies,<sup>43–47</sup> and a meta-analysis of DMARD data.<sup>48</sup>

Five cases of HZ were reported in patients receiving tofacitinib 5 mg BID in the first 3 months of the phase 3 studies, with 2 cases reported for placebo-treated patients (327.9 vs. 174.1 patient-years of exposure, respectively); no cases of HZ were reported in adalimumab-treated patients in ORAL Standard. This is consistent with higher nonserious HZ rates observed with all tofacitinib doses compared with placebo throughout the clinical development program.<sup>32,49</sup> Herpes zoster has generally been reported more frequently with tofacitinib than other DMARDs,<sup>37,38</sup> and it is interesting to note that HZ rates in phase 3 studies and LTE studies (after phase 3 study participation) were higher for patients receiving placebo (phase 3 studies only), adalimumab (phase 3 studies only), and tofacitinib (5 and 10 mg BID; phase 3 and LTE studies) compared with rates reported for other DMARDs.<sup>23,34</sup> Although the reasons for higher rates

remain unclear, HZ incidence may vary by race and region,<sup>50</sup> with more frequent reports among patients from Japan and Korea.<sup>32,34</sup> Rheumatoid arthritis is known to increase HZ infection risk, and some RA therapies may further increase this risk.<sup>51,52</sup> However, conflicting reports exist, and it remains unclear whether direct associations exist between RA therapies and HZ risk.<sup>32</sup>

Although no TB cases were reported in the tofacitinib 5 mg BID groups in the 5 phase 3 studies, cases have been reported in LTE studies,<sup>33</sup> and TB incidence across the tofacitinib clinical development program (5 and 10 mg BID) is known to be generally similar to TNFi and csDMARDs<sup>33,34,53–62</sup> and higher in countries with high background prevalence.<sup>33</sup> Comparisons of OI rates between studies are not straightforward because different studies use varying definitions of OI, and endemic infections vary by country.

Across the 5 phase 3 studies, 8 patients had malignancies (excluding NMSC), 6 patients had NMSC, and 2 patients had lymphoma in the tofacitinib 5 mg BID groups (1311.5 patient-years of exposure). Increased risks and incidence rates for malignancies and lymphomas have been associated with RA.<sup>31,37,39,63–76</sup> The types of malignancies reported in these studies and across the whole tofacitinib clinical development program<sup>31,77</sup> were similar to those reported for RA and general populations.<sup>31,64</sup>

No cases of gastrointestinal (GI) perforation were reported in patients treated with tofacitinib 5 mg BID across the 5 phase 3 studies (5945 patient-years of exposure). However, cases have been reported in other tofacitinib studies (3, 5, and 10 mg BID), including open-label LTE studies.<sup>23</sup> The background incidence rate for GI perforation with tofacitinib is similar to reported rates for csDMARDs and bDMARDs.<sup>23,78,79</sup>

Initial changes in laboratory parameters in the phase 3 studies were generally consistent with phase 2b observations,<sup>18,20</sup> and stabilization continues with longer-term treatment.<sup>23,80</sup> It is unclear whether neutrophil count decreases with tofacitinib and adalimumab are associated with increases in infectious AE rates, although, where reported in the phase 3 studies, none of the moderate to severe neutropenia cases with tofacitinib 5 mg BID were associated with SIEs. Decreases in mean lymphocyte levels were observed in the phase 3 studies, and although not assessed in phase 3 studies, in LTE studies rates of SIEs were increased in patients with confirmed lymphocyte counts of less than  $0.5 \times 10^3/\text{mm}^3$ .<sup>34</sup> It remains unclear whether lipid level changes associated with immune-modulatory therapy are associated with increased cardiovascular risks or whether increases in cardiovascular events are due to RA. Cardiovascular event rates in tofacitinib LTE studies are similar to published csDMARD and bDMARD rates.<sup>23,81–83</sup> Changes in serum creatinine and liver aminotransferase levels were small and consistent across all groups in all 5 studies. Pooled analyses and LTE studies have shown that reported tofacitinib-associated changes in serum creatinine levels and liver transaminases are reversible.<sup>23</sup> In addition, tofacitinib-related serum creatinine changes do not appear to be associated with acute renal failure or progressive worsening of renal function.<sup>23,84,85</sup>

These studies are limited by the relatively short placebo-controlled period, making analysis and interpretation of differences between active treatment and placebo difficult. However, this is an inherent issue when active treatment cannot be reasonably withheld for ethical reasons. These phase 3 studies were also relatively short in duration compared with the chronic duration of RA; however, long-term tofacitinib safety and efficacy continue to be monitored in an ongoing LTE study,<sup>23</sup> postmarketing surveillance,<sup>86</sup> and analyses of real-world data.<sup>87</sup> In addition, no specific screening methods were used to detect malignancies in any of these trials, so underlying malignancies may not be captured in the data. Patients who developed malignancies were required to discontinue, so it was not possible to assess

the risk of tofacitinib treatment on the development of additional malignancies.

Although we have observed and discussed similarities and differences in the safety and efficacy profiles of tofacitinib 5 mg BID to csDMARDs and bDMARDs reported in the literature, our comparisons are not based on head-to-head studies and should be interpreted with caution.

This comprehensive review of phase 3 data demonstrates that, in patients with DMARD-IR, tofacitinib 5 mg BID reduced the signs and symptoms of RA and improved physical function during the first 3 months of treatment. Improvements were sustained to month 6, similar to adalimumab with MTX in ORAL Standard and to other DMARDs across studies. Tofacitinib 5 mg BID demonstrated a consistent, manageable safety profile across the phase 3 studies. Patients should be monitored for AEs of special interest, including SIEs, OIs, malignancies and lymphomas, GI perforations, cardiovascular events, and changes in laboratory parameters. Monitoring of long-term tofacitinib safety and efficacy is ongoing in LTE studies, postmarketing surveillance, and analyses of real-world data.

## KEY POINTS

- We performed a comprehensive review of phase 3 studies of tofacitinib 5 mg BID, the widely approved dose, in patients with moderate to severe RA and DMARD-IR.
- In phase 3 studies, tofacitinib 5 mg BID reduced the signs and symptoms of RA and improved physical function.
- Tofacitinib 5 mg BID demonstrated a consistent, manageable safety profile across the phase 3 studies.

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