




ORIGINAL RESEARCH

Efficacy of tofacitinib in patients with rheumatoid arthritis stratified by baseline body mass index: an analysis of pooled data from phase 3 studies

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ABSTRACT

Objective Tofacitinib is an oral Janus kinase for the treatment of rheumatoid arthritis (RA). This post hoc analysis assessed whether baseline body mass index (BMI) impacts tofacitinib efficacy in patients with RA.

Methods Pooled data from six phase 3 studies in patients receiving tofacitinib 5 mg (N=1589) or 10 mg (N=1611) twice daily or placebo (advancing to active treatment at months 3 or 6; N=680), ±conventional synthetic disease-modifying antirheumatic drugs, were stratified by baseline BMI (<25, 25 to <30, ≥30 kg/m²). Endpoints (through to month 6) were assessed descriptively: American College of Rheumatology 20/50/70 response rates; changes from baseline (Δ) in Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4(ESR)), DAS28-4(C-reactive protein), Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire-Disability Index (HAQ-DI) and pain; and proportions of patients achieving DAS28-4(ESR) ≥1.2 and HAQ-DI ≥0.22 decreases from baseline, low disease activity (DAS28-4(ESR) ≤3.2 or CDAI ≤10) and radiographic non-progression (Δmodified Total Sharp Score ≤0.5; months 12 and 24). Estimates were adjusted using multivariable models for selected outcomes. Univariate/multivariable regression analyses determined predictors of month 6 outcomes.

Results Of 3880 patients included, 1690 (43.6%), 1173 (30.2%) and 1017 (26.2%) had baseline BMI <25, 25 to <30 and ≥30 kg/m², respectively. Tofacitinib showed greater efficacy improvements versus placebo in each BMI category. Differences in efficacy outcomes (adjusted and unadjusted) were generally not clinically meaningful across BMI categories within treatment groups. In regression analyses, BMI was not consistently associated with selected outcomes.

Conclusions Baseline BMI did not consistently affect tofacitinib response suggesting that tofacitinib is an effective oral treatment option for adults with moderate to severe RA regardless of baseline BMI, including patients with BMI ≥30 kg/m².

Trial registration numbers NCT00814307, NCT01039688; NCT00960440; NCT00847613; NCT00856544; NCT00853385.

Key messages

What is already known about this subject?

⇒ Previous analyses have shown that some biologic therapies (eg, tumour necrosis factor inhibitors) for rheumatoid arthritis (RA) are associated with an attenuated clinical response in patients with obesity.

What does this study add?

⇒ In contrast to what is known for some biologic therapies, this analysis of pooled data from six phase 3 randomised trials of tofacitinib in patients with RA demonstrates that differences in clinical efficacy outcomes with tofacitinib were generally negligible across baseline body mass index (BMI) categories.
⇒ Treatment with tofacitinib 5 and 10 mg twice daily led to improvements in efficacy outcomes versus placebo irrespective of baseline BMI.

How might this impact on clinical practice or further developments?

⇒ The results of this analysis further inform clinical decision-making of tofacitinib as a treatment option for patients with moderate to severe RA by showing that the efficacy of tofacitinib was comparable across BMI categories.

INTRODUCTION

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). The efficacy and safety of tofacitinib 5 and 10 mg twice daily administered as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), mainly methotrexate (MTX), in adult patients with moderately to severely active RA, have been demonstrated in phase 2,¹⁻⁵ phase 3⁶⁻¹¹ and phase 3b/4¹²⁻¹³ randomised controlled trials (RCTs) with up to 72 months of follow-up and in long-term extension studies with up to 9.5 years of observation.¹⁴⁻¹⁶

Evidence suggests that the efficacy of some RA treatments is impacted by body mass index (BMI). Lower response and/or remission rates with increasing BMI have been reported with csDMARDs (including MTX), sarilumab and some tumour necrosis factor inhibitors (TNFi; eg, adalimumab, etanercept and infliximab), with outcomes most affected in patients with obesity (generally defined as a BMI ≥ 30 kg/m²).^{17–20} Obesity is characterised by low-grade systemic inflammation, and is associated with increased production of proinflammatory cytokines, including TNF and interleukin-6,²¹ and altered expression of adipokines, such as leptin, resistin and adiponectin.²² In patients with RA, obesity appears to be associated with less radiographic progression and structural damage, which may be due to various factors, including body mass and adipokine levels.^{23–26}

This post hoc analysis of data from the tofacitinib RA clinical development programme assessed whether baseline BMI impacts the efficacy of tofacitinib 5 mg twice daily (the recommended dosage for RA) and 10 mg twice daily in adult patients with moderate to severe RA.

PATIENTS AND METHODS

Study design

Data were pooled from six double-blind phase 3 RCTs from the tofacitinib RA clinical development programme (online supplemental table 1). Full eligibility criteria have been reported for each study.^{6–11}

Patients

Eligible patients were aged ≥ 18 years with a diagnosis of RA and met the American College of Rheumatology (ACR) 1987 Revised RA Classification Criteria. Patients were randomised to receive tofacitinib 5 or 10 mg twice daily, placebo (advancing to tofacitinib at months 3 or 6), or the active controls MTX (ORAL Start) or adalimumab (ORAL Standard).

Assessments and outcomes

BMI was calculated for each patient as weight (in kilograms (kg))/height (in metres (m)²) at baseline only. Patients were stratified by baseline BMI: < 25 (underweight/normal); 25 to < 30 (overweight); and ≥ 30 kg/m² (obese).

Endpoints assessed included: ACR $\geq 20\%$, $\geq 50\%$, or $\geq 70\%$ response criteria (ACR20/50/70 response rates) at months 3 and 6; mean changes from baseline through to month 6 in Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4(ESR)), DAS28-4, C-reactive protein (DAS28-4(CRP)), Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire-Disability Index (HAQ-DI) and pain (Visual Analogue Scale (VAS)); the proportion of patients reporting improvements \geq minimum clinically important difference (MCID) in DAS28-4 (ESR) (decrease from baseline ≥ 1.2) and HAQ-DI (decrease from baseline ≥ 0.22) at months 3 and 6; proportions of patients achieving low disease activity (LDA) at months 3 and 6 as defined by

DAS28-4(ESR) ≤ 3.2 or CDAI ≤ 10 ; and the proportion of patients with no radiographic progression, defined as change from baseline in modified Total Sharp Score ≤ 0.5 at months 12 and 24 (pooled data from ORAL Scan and ORAL Start only).

An additional analysis of select outcomes (ACR20/50/70 response rates, changes from baseline in DAS28-4(ESR), CDAI and HAQ-DI, and DAS28-4(ESR)-defined and CDAI-defined LDA) was performed in which patients were stratified by baseline body weight: < 60 , 60 to < 90 and ≥ 90 kg.

Statistical analysis

Descriptive analyses

Analyses were performed on the full analysis set, which included patients who were randomised and received ≥ 1 dose of study treatment. Efficacy analyses at month 3 used a 'pure' placebo group (ie, all patients received placebo), whereas the placebo group at month 6 included patients receiving placebo through to month 3 but who advanced to tofacitinib from month 3 to month 6 per protocol.

ACR response rates were assessed using both non-responder imputation (NRI) and observed data. NRI was also used for the rates of achievement of improvements \geq MCID and LDA, while observed data were used for rates of radiographic non-progression and for continuous endpoints. For binary endpoints, comparisons between active treatment groups and placebo were conducted using a normal approximation for binomial proportions with Z-scores to test for statistical significance; continuous endpoints are presented descriptively. No multiplicity adjustment was performed in this post hoc analysis.

Statistical modelling

Regression models were run with treatment group, BMI and treatment by BMI interaction terms to assess consistency of the relationship between BMI and efficacy response across treatments.

Univariate logistic regression analyses (for ACR50 response) and univariate regression analyses (for changes from baseline in DAS28-4(ESR), DAS28-4(CRP), CDAI and HAQ-DI) were performed to determine the relationship between each baseline covariate (described below) and each efficacy endpoint. Multivariable logistic regression analyses (for ACR50 response) and multivariable regression analyses (for changes from baseline in DAS28-4(ESR), DAS28-4(CRP), CDAI, and HAQ-DI) were performed to determine potential predictors for each efficacy endpoint based on a stepwise selection method using 5% level of significance. In both univariate and multivariable analyses, baseline BMI was assessed as both a categorical (ie, BMI < 25 , 25 to < 30 , and ≥ 30 kg/m²) and a continuous variable.

Baseline BMI, age, gender and baseline value of the response variable (for continuous response variables) were forced to be included in the multivariable models. Other baseline covariates considered as candidates for the model selection included glucocorticoid use, history of myocardial infarction, MTX use, race, smoking history,

prior TNFi failure, seropositivity (positive for rheumatoid factor and/or anti-cyclic citrullinated peptide antibody), HAQ-DI score, pain (VAS), swollen joint count (SJC), tender joint count (TJC), opioid use and somatisation comorbidity phenotype. The somatisation comorbidity phenotype was defined by the use of concomitant medications for the treatment of depression, anxiety or neuropathic pain, or an ongoing baseline medical diagnosis of depression, chronic pain, fibromyalgia or myalgias. It indicates patients who may have at least one condition, other than RA, that may contribute to chronic pain (eg, fibromyalgia) or that could have influenced pain and the patient's self-management of their RA (eg, depression).²⁷

Adjusted estimates for specified outcomes by baseline BMI category were calculated based on the multivariable regression analyses. For binary outcomes (ACR20/50/70 response rates at month 6, and radiographic non-progression at month 24), a fitted logistic regression model²⁸ was used to predict the response rate for every patient in the BMI categories being compared (≥ 25 to <30 and ≥ 30 kg/m², compared with BMI <25 kg/m²) as if they had been in a specified BMI category or the reference BMI category, and the differences in the average of the rates by BMI category were computed. For continuous outcomes (change from baseline at month 6 in HAQ-DI, DAS28-4(ESR), DAS28-4(CRP) and CDAI), an analysis of covariance model was run for each endpoint for each tofacitinib dose, with least squares means, mean differences of BMI 25 to <30 and ≥ 30 kg/m² from BMI <25 kg/m², and 95% CIs calculated. All models used the covariates described above, except somatisation comorbidity phenotype, which was not associated with any outcome for either tofacitinib dose in the regression analyses; baseline value of the response variable included for continuous response variables only. Observed data were used and missing values were not imputed.

Additionally, sensitivity analyses were performed using the stepwise multivariable regression analysis and the least absolute shrinkage and selection operator (Lasso) regression method with the lambda plus 1se criterion (ie, the largest value of the tuning parameter lambda such that the error is within one SE of the minimum),²⁹ where no variables were forced into both models.

For all analyses, clinical relevance was defined based on the magnitude of the published MCID for each outcome measure; a difference from the baseline BMI <25 kg/m² category (reference) of: $\geq 10\%$ for binary outcomes (eg, ACR50); ≥ 1.2 units for DAS28-4(ESR)³⁰; ≥ 1.0 units for DAS28-4(CRP)³⁰; ≥ 12 units for CDAI^{30,31}; ≥ 20 units in pain (0–100 mm VAS)³⁰ and ≥ 0.22 units for HAQ-DI.³²

RESULTS

Patients

This post hoc analysis included 3880 patients receiving tofacitinib 5 mg twice daily (n=1589; 41.0%), tofacitinib 10 mg twice daily (n=1611; 41.5%) and placebo (n=680; 17.5%) stratified by baseline BMI; of these, 1690 (43.6%),

1173 (30.2%) and 1017 (26.2%) patients had baseline BMI values of <25 , 25 to <30 , and ≥ 30 kg/m², respectively.

Baseline demographics and disease characteristics (table 1; online supplemental table 2) were generally similar within each BMI category across treatment groups; however, numeric differences were observed between BMI categories. Irrespective of treatment group, patients in the BMI <25 kg/m² category were younger and were more likely to be Asian and to never have smoked, compared with the higher BMI categories (25 to <30 and ≥ 30 kg/m²). In contrast, a higher proportion of patients with BMI ≥ 30 kg/m² were Caucasian, from the USA, and were ex-smokers, versus patients with BMI <25 and 25 to <30 kg/m²; patients with BMI ≥ 30 kg/m² were also slightly less likely to be seropositive. Baseline mean TJC, SJC, HAQ-DI and pain (VAS) scores were higher as BMI category increased.

Higher rates of diabetes, hypertension and prior use of TNFi were observed in patients with BMI ≥ 30 kg/m² than patients in the lower BMI categories.

Efficacy outcomes stratified by BMI

Covariate-adjusted estimates for ACR20/50/70 response rates with both tofacitinib doses at month 6 were not significantly different in the BMI 25 to <30 and ≥ 30 kg/m² categories compared with the BMI <25 kg/m² category (figure 1). An exception was the estimated ACR70 response rate in the tofacitinib 5 mg twice daily group, which was significantly lower in the BMI 25 to <30 kg/m² category, but this difference was $<10\%$ and therefore was not considered clinically relevant.

Additionally, at months 3 and 6, ACR20/50/70 response rates (assessed using NRI) were significantly higher in patients receiving either tofacitinib dose versus placebo ($p<0.05$), regardless of baseline BMI category (online supplemental figure 1). In general, there appeared to be a numeric trend towards somewhat lower ACR20/50/70 response rates at both months 3 and 6 with increasing baseline BMI in patients receiving tofacitinib 5 and 10 mg twice daily; however, the differences between BMI categories were generally $<10\%$ and were not considered clinically meaningful (online supplemental figure 1). Similar trends were observed when ACR20/50/70 response rates were assessed using observed data (data not shown). Overall, the trends were less clear for patients receiving placebo, particularly for ACR50/70 response rates.

In general, adjusted estimates for the least squares mean changes from baseline in DAS28-4(ESR), DAS28-4(CRP), CDAI and HAQ-DI with both tofacitinib doses at month 6 were not significantly different with BMI 25 to <30 and ≥ 30 versus <25 kg/m² (figure 2). Exceptions included mean decreases in DAS28-4(ESR) and DAS28-4(CRP) (with tofacitinib 10 mg twice daily) and HAQ-DI (with tofacitinib 5 mg twice daily), which were significantly smaller in patients with baseline BMI ≥ 30 versus <25 kg/m²; these differences were not clinically relevant.

Table 1 Demographics and baseline disease characteristics

	Tofacitinib 5 mg twice daily (N=1589)		Tofacitinib 10 mg twice daily (N=1611)		Placebo (N=680)	
	<25 (N1=686)	≥30 (N1=388)	<25 (N1=696)	≥30 (N1=472)	<25 (N1=308)	≥30 (N1=186)
BMI category, kg/m²	25 to <30 (N1=515)	≥30 (N1=388)	25 to <30 (N1=472)	≥30 (N1=443)	25 to <30 (N1=186)	≥30 (N1=186)
Age in years, mean (SD)	54.1 (11.4)	53.9 (9.9)	49.6 (12.9)	53.0 (11.6)	50.4 (12.8)	53.7 (10.1)
Race, n (%)						
White	327 (47.7)	313 (80.7)	337 (48.4)	326 (69.1)	139 (45.1)	144 (77.4)
Black	10 (1.5)	23 (5.9)	8 (1.2)	12 (2.5)	11 (3.6)	2 (1.1)
Asian	283 (41.3)	21 (5.4)	284 (40.8)	73 (15.5)	133 (43.2)	9 (4.8)
Other	66 (9.6)	31 (8.0)	67 (9.6)	61 (12.9)	25 (8.1)	11 (5.9)
Geographic region, n (%)						
USA	67 (9.8)	142 (36.6)	60 (8.6)	92 (19.5)	29 (9.4)	44 (23.7)
Latin America	94 (13.7)	59 (15.2)	104 (14.9)	91 (19.3)	43 (14.0)	30 (16.1)
Europe/Canada	226 (32.9)	147 (37.9)	224 (32.2)	195 (41.3)	97 (31.5)	86 (46.2)
Rest of world	299 (43.6)	40 (10.3)	308 (44.3)	94 (19.9)	139 (45.1)	26 (14.0)
Smoking history, n (%)						
Never smoked	501 (73.0)	209 (53.9)	520 (74.7)	307 (65.0)	220 (71.4)	103 (55.4)
Smoker	101 (14.7)	78 (15.2)	111 (16.0)	96 (20.3)	53 (17.2)	33 (17.7)
Ex-smoker	84 (12.2)	93 (18.1)	65 (9.3)	69 (14.6)	33 (10.7)	52 (28.0)
TJC, mean (SD)	24.6 (14.3)	26.9 (14.9)	24.1 (14.4)	25.9 (14.3)	23.5 (13.6)	29.9 (16.6)
SJC, mean (SD)	14.7 (8.7)	15.7 (9.0)	14.7 (8.4)	15.6 (8.9)	14.5 (8.5)	17.1 (10.6)
HAQ-DI, mean (SD)	1.4 (0.7)	1.5 (0.7)	1.4 (0.7)	1.5 (0.7)	1.4 (0.7)	1.6 (0.6)
DAS28-4(ESR), mean (SD)	6.5 (1.0)	6.5 (1.0)	6.4 (1.0)	6.4 (1.0)	6.4 (1.0)	6.5 (1.0)
DAS28-4(CRP), mean (SD)	5.6 (1.0)	5.7 (1.0)	5.6 (1.0)	5.6 (1.0)	5.5 (1.0)	5.8 (1.0)
Pain (VAS), mean (SD)	57.6 (23.4)	60.3 (23.9)	58.5 (23.0)	60.3 (23.9)	56.8 (23.0)	59.5 (22.2)
CRP, mg/L, mean (SD)	20.0 (24.8)	18.8 (24.8)	19.2 (23.0)	18.0 (25.9)	17.1 (20.0)	15.2 (17.3)
(median) (Q1, Q3)	(9.7)	(9.3)	(10.0)	(3.5, 25.3)	(4.3, 24.3)	(8.9)
	(3.8, 27.6)	(4.3, 24.1)	(3.9, 25.6)	(5.3, 21.0)	(5.3, 21.0)	(4.9, 19.1)
RF+, n (%)	517 (75.6)	387 (76.5)	516 (74.4)	347 (73.8)	210 (68.4)	112 (60.5)
Anti-CCP+, n (%)	565 (82.8)	396 (78.0)	545 (78.5)	359 (76.6)	246 (81.2)	119 (64.3)
Diabetes, n (%)	31 (4.5)	44 (8.5)	24 (3.5)	46 (9.8)	12 (3.9)	25 (13.4)
Hypertension, n (%)	156 (22.7)	192 (37.3)	153 (22.0)	165 (35.0)	70 (22.7)	99 (53.2)
Prior TNFi, n (%)	103 (15.0)	97 (18.8)	108 (15.5)	74 (15.7)	63 (20.5)	87 (46.8)

Continued

Table 1 Continued

	Tofacitinib 5 mg twice daily (N=1589)	Tofacitinib 10 mg twice daily (N=1611)	Placebo (N=680)
BMI category, kg/m²	<25 (N1=686) 25 to <30 (N1=515)	<25 (N1=696) 25 to <30 (N1=472)	<25 (N1=308) 25 to <30 (N1=186)
	>=30 (N1=388)	>=30 (N1=443)	>=30 (N1=186)

N1 values may vary for each outcome based on the number of patients assessed. BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, C-reactive protein; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; DAS28-4(ESR+CRP), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; n, number of patients with characteristic; N, number of patients in each treatment group with a baseline BMI value; N1, number of patients in each BMI category; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitors; VAS, Visual Analogue Scale.

Regardless of BMI category, mean changes from baseline (using descriptive analyses of observed data) at months 3 and 6 in DAS28-4(ESR), DAS28-4(CRP), CDAI, HAQ-DI and pain (VAS) were greater for patients receiving either tofacitinib dose versus placebo (online supplemental figures 2 and 3). Differences in mean changes from baseline through to month 6 in each efficacy endpoint were small and not clinically relevant, based on the definitions used in this analysis, across baseline BMI categories for patients receiving tofacitinib 5 or 10 mg twice daily, or placebo (online supplemental figures 2 and 3).

The proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved improvements \geq MCID in DAS28-4(ESR) and HAQ-DI (decreases ≥ 1.2 and ≥ 0.22 , respectively) at months 3 and 6 were generally similar regardless of baseline BMI (online supplemental figure 4A,B). The proportion of patients achieving DAS28-4(ESR)-defined and CDAI-defined LDA (≤ 3.2 and ≤ 10 , respectively) with tofacitinib 5 and 10 mg twice daily and placebo, were generally similar across baseline BMI categories at months 3 and 6 (online supplemental figure 4C,D).

Adjusted estimates for the differences in rates of radiographic non-progression with tofacitinib 5 mg twice daily at month 24 were not significantly different in the baseline BMI 25 to <30 and ≥ 30 kg/m² categories versus the BMI <25 kg/m² category. In the tofacitinib 10 mg twice daily group, significantly higher rates of non-progression were observed in patients with baseline BMI ≥ 30 versus <25 kg/m² (figure 1D).

In unadjusted analyses, the proportions of patients with radiographic non-progression at months 12 and 24 (based on patients pooled from ORAL Scan and ORAL Start studies) showed a trend towards higher rates of non-progression with higher baseline BMI in patients treated with tofacitinib 10 mg twice daily (online supplemental figure 5).

Efficacy outcomes stratified by weight

An analysis was performed whereby patients were stratified by weight (<60, 60 to 90, ≥ 90 kg) rather than BMI, and assessed proportions of patients achieving ACR20/50/70 responses, DAS28-4(ESR)-defined and CDAI-defined LDA, and changes from baseline in DAS28-4(ESR), CDAI and HAQ-DI. Results were similar to the analyses of efficacy stratified by BMI (data not shown).

Univariate modelling analyses

Results of the univariate modelling analyses (online supplemental table 3) showed that categorical BMI was a significant predictor for ACR50 response and change from baseline in DAS28-4(ESR) (both for tofacitinib 10 mg twice daily only), whereas continuous BMI was a significant predictor for ACR50 response (both tofacitinib doses), and changes from baseline in DAS28-4(ESR) (both tofacitinib doses), DAS28-4(CRP) (tofacitinib 10 mg twice daily only) and HAQ-DI (tofacitinib 5 mg twice daily only). Neither categorical nor continuous BMI were significant predictors for

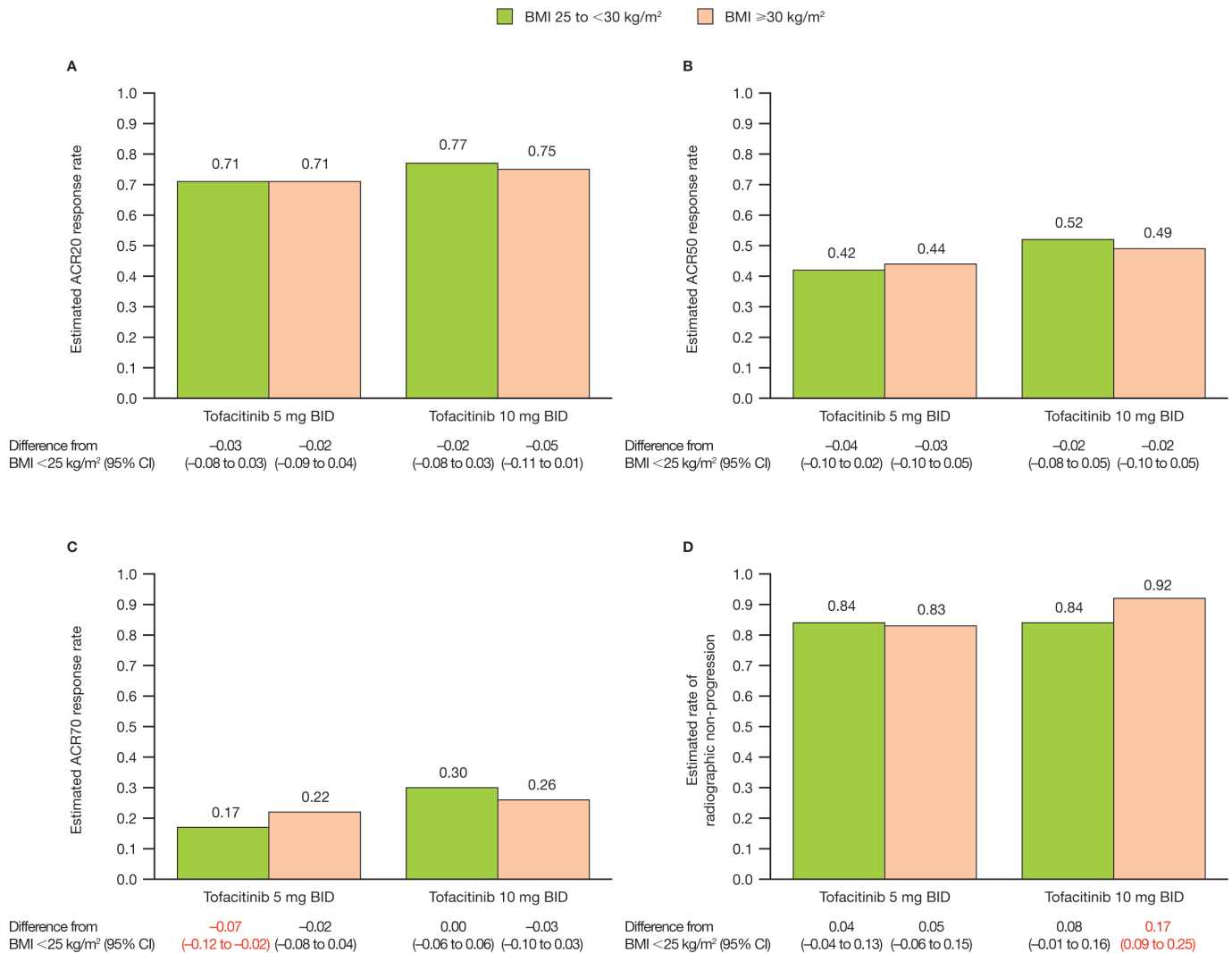


Figure 1 Adjusted estimates for differences between BMI categories in (A) ACR20, (B) ACR50 and (C) ACR70 response rates at month 6 and (D) rates of radiographic non-progression (change from baseline in mTSS ≤ 0.5) at month 24 (FAS, no imputation). Based on logistic regression model that includes the variables: age, gender, baseline BMI, baseline HAQ-DI score, race, smoking history, baseline glucocorticoid use, history of myocardial infarction, prior TNFi failure, seropositivity, baseline methotrexate use, baseline opioid use, baseline pain (VAS), baseline swollen joint count and baseline tender joint count. Red text indicates statistical significance for difference from BMI <25 kg/m² as 95% CI does not include 0. For this analysis, a difference from the baseline BMI <25 kg/m² category (reference) of ≥ 0.10 was considered clinically meaningful. ACR, American College of Rheumatology; BID, twice daily; BMI, body mass index; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, modified Total Sharp Score; TNFi, tumour necrosis factor inhibitors; VAS, Visual Analogue Scale.

change from baseline in CDAI. Where BMI was a significant predictor for response, the response generally worsened with increasing BMI, although the effect was small.

Multivariable regression analyses

The models that included BMI by treatment interaction showed insufficient evidence to conclude that there was inconsistency in the relationship between BMI and efficacy response across treatments (data not shown), thus an interaction term was not included in subsequent models. Results of the stepwise multivariable-adjusted regression analyses showed little evidence that categorical BMI was a significant predictor for most response variables for either tofacitinib dose. Continuous BMI was a significant

predictor for several outcomes although this was of small magnitude (table 2). Generally, BMI (both as categorical and continuous variable) was not a significant predictor for most of the response variables, with the exception of change from baseline in HAQ-DI for tofacitinib 5 mg twice daily and change from baseline in DAS28-4(CRP) for tofacitinib 10 mg twice daily, although changes were small. Additionally, continuous BMI was a significant predictor for ACR50 response and change from baseline in DAS28-4(ESR) for tofacitinib 10 mg twice daily. Where BMI was a significant predictor for response, the response generally worsened with increasing BMI. Continuous baseline response variables (which had been forced into

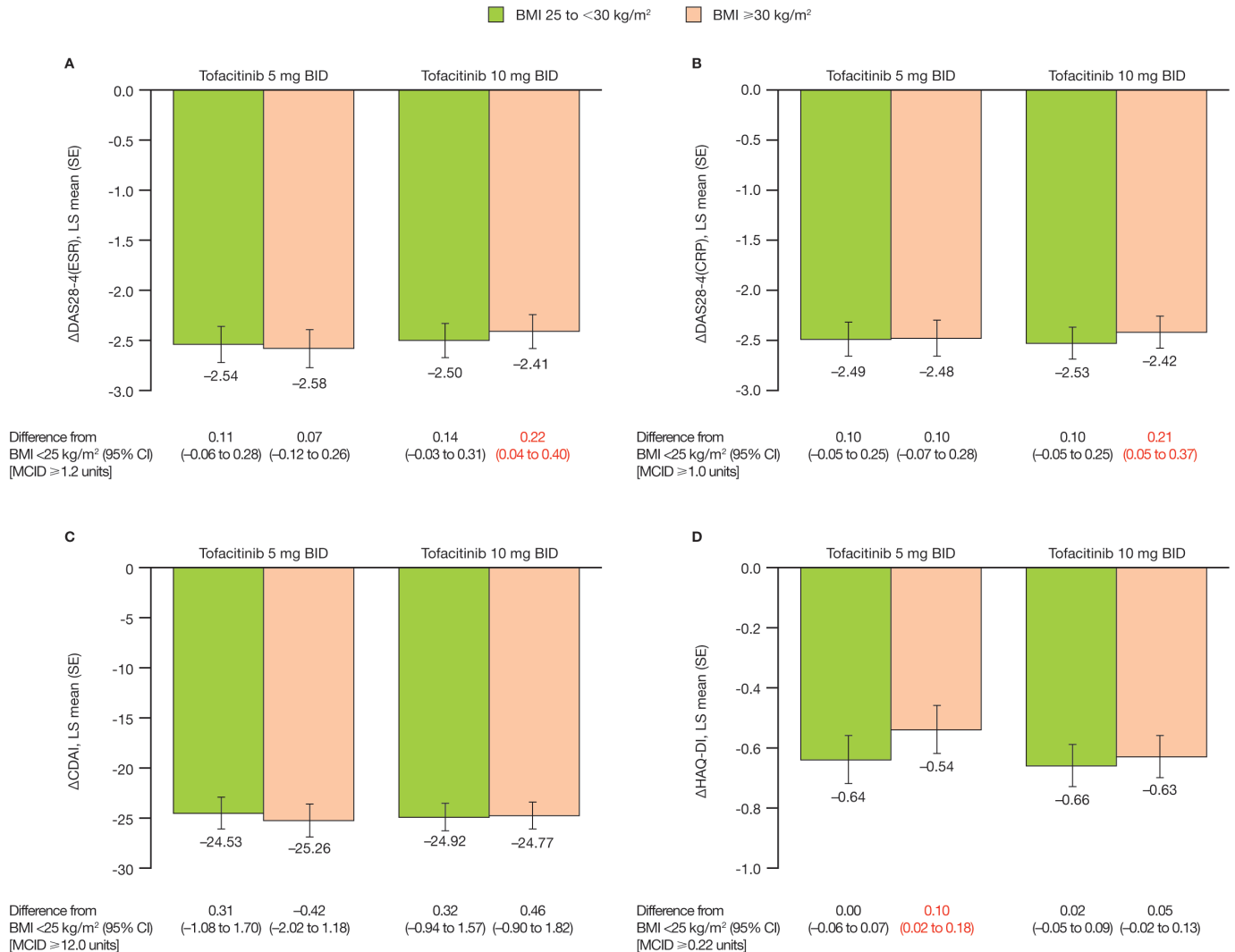


Figure 2 Adjusted estimates for LS mean differences (ANCOVA) between BMI categories in change from baseline in (A) DAS28-4(ESR), (B) DAS28-4(CRP), (C) CDAI and (D) HAQ-DI at month 6 (FAS, no imputation). Based on ANCOVA model that includes the variables: age, gender, baseline BMI, baseline HAQ-DI score, baseline value of the response variable, race, smoking history, baseline glucocorticoid use, history of myocardial infarction, prior TNFi failure, seropositivity, baseline methotrexate use, baseline opioid use, baseline pain (VAS), baseline swollen joint count, and baseline tender joint count. Red text indicates statistical significance for difference from BMI <25 kg/m² as 95% CI does not include 0. For this analysis, a difference from the baseline BMI <25 kg/m² category (reference) of ≥1.2 (DAS28-4(ESR)), ≥1.0 (DAS28-4(CRP)), ≥12 (CDAI)³⁰ and ≥0.22 (HAQ-DI)³² were considered clinically meaningful. Δ, change from baseline; ANCOVA, analysis of covariance; BID, twice daily; BMI, body mass index; CDAI, Clinical Disease Activity Index; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; MCID, minimum clinically important difference; TNFi, tumour necrosis factor inhibitors; VAS, Visual Analogue Scale.

the model) and seropositivity were significant for all efficacy endpoints; somatisation comorbidity phenotype was not a significant predictor for any endpoint (table 2).

Sensitivity analysis results of the stepwise multivariable regression analyses (with no forced variables) showed that in most cases, BMI was not selected in the final model (online supplemental table 4). In cases where it was selected, the magnitude of the effect was not clinically significant, and was smaller than the MCID of the outcome. Lasso regression with a lambda 1se selection criterion produced generally similar results to the stepwise regression model with regard to selection of BMI in

the final model (ie, BMI was usually not selected). In the few models where the Lasso model did select BMI, the magnitude of its effect was negligible.

DISCUSSION

This post hoc analysis of pooled data from six phase 3 RCTs aimed to assess the impact of baseline BMI (<25, 25 to <30 and ≥30 kg/m²) on the efficacy of tofacitinib in patients with moderate to severe RA. These findings showed that treatment with tofacitinib 5 and 10 mg twice daily led to improvements in efficacy outcomes

Table 2 Multivariable model results using stepwise selection method* (with continuous BMI†) summarising OR (95% CI) for ACR50 response and estimate‡ (95% CI) for continuous outcomes at month 6

Tofacitinib dose (twice daily)	ACR50 response		ΔDAS28-4(ESR)		ΔDAS28-4(CRP)		ΔCDAI		ΔHAQ-DI	
	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg
BMI category,† kg/m ²										
25 to <30 versus <25	0.87 (0.67 to 1.12)	0.90 (0.69 to 1.16)	0.09 (-0.07 to 0.26)	0.11 (-0.05 to 0.26)	0.11 (-0.04 to 0.26)	0.11 (-0.04 to 0.26)	0.32 (-1.06 to 1.70)	0.36 (-0.90 to 1.61)	0.01 (-0.06 to 0.08)	0.02 (-0.05 to 0.09)
≥30 versus <25	0.94 (0.71 to 1.25)	0.80 (0.61 to 1.04)	0.07 (-0.11 to 0.25)	0.19 (0.03 to 0.36)	0.14 (-0.03 to 0.30)	0.21 (0.06 to 0.37)	-0.37 (-1.95 to 1.21)	0.44 (-0.91 to 1.79)	0.10 (0.03 to 0.18)	0.06 (-0.02 to 0.13)
BMI*	0.99 (0.98 to 1.01)	0.98 (0.96 to 1.00)	0.01 (-0.01 to 0.02)	0.02 (0.01 to 0.03)	0.01 (0.00 to 0.02)	0.02 (0.01 to 0.03)	-0.03 (-0.13 to 0.07)	0.05 (-0.04 to 0.14)	0.01 (0.00 to 0.01)	0.00 (0.00 to 0.01)
Glucocorticoid use						0.14 (0.01 to 0.26)			0.07 (0.01 to 0.13)	
History of myocardial infarction			-0.73 (-1.38 to -0.09)		-0.84 (-1.45 to -0.23)		-6.99 (-12.60 to -1.39)			
MTX use		0.78 (0.62 to 0.96)		0.26 (0.12 to 0.39)		0.21 (0.09 to 0.34)		1.52 (0.49 to 2.55)	0.14 (0.08 to 0.20)	0.14 (0.09 to 0.20)
Gender* (male vs female)	1.32 (0.99 to 1.75)	1.32 (0.99 to 1.77)	-0.45 (-0.64 to -0.29)	-0.47 (-0.65 to -0.27)	-0.20 (-0.37 to -0.03)	-0.14 (-0.31 to 0.02)	-1.95 (-3.49 to -0.40)	-0.93 (-2.33 to 0.48)	-0.14 (-0.21 to -0.06)	-0.10 (-0.18 to -0.02)
Race										
White versus others							2.86 (0.88 to 4.85)	2.81 (1.13 to 4.49)	0.13 (0.03 to 0.23)	0.14 (0.04 to 0.23)
Black versus others							0.72 (-2.91 to 4.34)	0.95 (-2.50 to 4.39)	0.07 (-0.12 to 0.25)	-0.03 (-0.22 to 0.15)
Asian versus others							2.00 (-0.18 to 4.18)	2.20 (0.29 to 4.10)	0.02 (-0.08 to 0.13)	-0.01 (-0.11 to 0.10)
Smoking status										
Smoker versus never smoked									0.09 (0.01 to 0.17)	
Ex-smoker versus never smoked										-0.07 (-0.15 to 0.02)
TNFi failure		0.70 (0.50 to 0.97)							0.12 (0.03 to 0.21)	0.14 (0.06 to 0.23)
Seropositivity (yes vs no)	1.66 (1.20 to 2.29)	1.53 (1.15 to 2.03)	-0.24 (-0.44 to -0.03)	-0.25 (-0.43 to -0.07)	-0.35 (-0.53 to -0.17)	-0.29 (-0.45 to -0.13)	-3.46 (-5.11 to -1.82)	-1.86 (-3.20 to -0.53)	-0.14 (-0.23 to -0.06)	-0.13 (-0.20 to -0.05)
HAQ-DI						0.16 (0.06 to 0.27)		1.07 (0.21 to 1.92)	-0.48\$ (-0.52 to -0.43)	-0.48\$ (-0.52 to -0.44)
Pain (VAS)		1.00 (1.00 to 1.01)			0.00 (0.00 to 0.01)		0.03 (0.00 to 0.06)			
SJC	1.03 (1.01 to 1.04)									0.00 (-0.01 to 0.00)

Continued

Table 2 Continued

Tofacitinib dose (twice daily)	ACR50 response		ΔDAS28-4(ESR)		ΔDAS28-4(CRP)		ΔCDAI		ΔHAQ-DI	
	5mg	10mg	5mg	10mg	5mg	10mg	5mg	10mg	5mg	10mg
TJC	0.99 (0.98 to 1.00)	0.01 (0.00 to 0.02)	0.01 (0.01 to 0.02)	0.01 (0.00 to 0.01)	0.02 (0.01 to 0.02)	0.02 (0.01 to 0.02)	0.17 (0.10 to 0.23)	0.09 (0.04 to 0.15)	0.01 (0.00 to 0.05)	0.01 (0.01 to 0.01)
Age*	0.99 (0.98 to 1.00)	0.99 (0.98 to 1.00)	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.01)	0.02 (-0.03 to 0.07)	0.00 (0.00 to 0.07)	0.01 (0.00 to 0.05)	0.01 (0.01 to 0.01)
Opioid use (yes vs no)	0.52 (0.35 to 0.76)	0.29 (0.06 to 0.52)	0.29 (0.06 to 0.52)	0.22† (0.02 to 0.42)	0.36 (0.15 to 0.57)	0.22† (0.02 to 0.42)	3.91 (1.98 to 5.84)	2.02 (0.31 to 3.74)	0.00 (0.00 to 0.05)	0.01 (0.01 to 0.01)
Corresponding baseline value of response variable*	N/A	N/A	-0.60 (-0.70 to -0.51)	-0.61 (-0.70 to -0.52)	-0.82 (-0.91 to -0.72)	-0.90 (-0.99 to -0.81)	-0.85 (-0.92 to -0.77)	-0.83 (-0.89 to -0.77)	-0.48 (-0.52 to -0.43)	-0.48 (-0.52 to -0.44)

Red text indicates statistical significance at $p < 0.05$. For categorical variables with more than two levels, the pairwise comparisons are considered significant if both the overall and pairwise p values are < 0.05 . Covariates with blank cells were not selected in the multivariable model.
 *Variables that were forced into the model included continuous BMI, age, gender and baseline value of the response variable.
 †Categorical BMI was forced into a separate model using the same set of covariates. The ORs and estimates of the outcomes in this model are similar to those of the model with continuous BMI, except where indicated.
 ‡For categorical BMI versus continuous outcomes, the estimate reflects the least squares mean difference between categories. For continuous BMI versus continuous outcomes, the estimate is the slope of the relationship.
 §Included as baseline value of response variable.
 ¶Included only in the model run with categorical BMI, but not the model with continuous BMI.
 Δ, change from baseline; ACR, American College of Rheumatology; BMI, body mass index; CDAI, Clinical Disease Activity Index; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; N/A, not applicable; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitors; VAS, Visual Analogue Scale.

versus placebo, irrespective of baseline BMI. Moreover, in adjusted analyses, differences in efficacy outcomes (ACR20/50/70 response rates, changes from baseline in DAS28-4(ESR), DAS28-4(CRP), CDAI and HAQ-DI) in patients with baseline BMI 25 to < 30 and ≥ 30 versus < 25 kg/m² were not clinically relevant. For the purposes of this analysis, thresholds for clinically relevant differences based on commonly used definitions and consistent with those used for MCIDs and in non-inferiority studies were considered.^{12 30 32 33} In unadjusted analyses, these efficacy outcomes, as well as pain (VAS) and rates of achieving \geq MCID in DAS28-4(ESR) (decreases ≥ 1.2) and HAQ-DI (decreases ≥ 0.22), and DAS28-4(ESR)-defined and CDAI-defined LDA were generally similar across baseline BMI categories within treatment groups, with some small numeric differences noted that were clinically irrelevant.

By contrast, patients with baseline BMI ≥ 30 kg/m² who received tofacitinib 10 mg twice daily showed higher rates of radiographic non-progression versus those with baseline BMI < 25 kg/m² in both adjusted and unadjusted analyses; these results were considered clinically relevant as the difference between groups exceeded the threshold defined for this analysis. Across treatments, patients with baseline BMI ≥ 30 kg/m² were less likely to be seropositive than those with lower BMI; seropositivity is associated with progression of structural damage.^{34 35} Additionally, a protective effect for synovitis and osteitis in patients with RA and obesity has previously been noted,^{23 36} although the reasons for this are unclear; this may be due to effects of adipokines such as adiponectin, levels of which are known to decrease with increased fat mass, and which may have proinflammatory activity in joints.²⁴ However, further research is warranted in this area.

In addition to these analyses, univariate and multivariable regression analyses were performed to investigate the relationship between selected baseline covariates and efficacy endpoints, and to identify potential predictors for these endpoints. Continuous BMI was selected in the final model for more variables than categorical BMI, which is not surprising given that the continuous model would be expected to be more sensitive. While BMI was selected in the multivariable regression analysis as a predictor for changes from baseline in HAQ-DI for tofacitinib 5 mg twice daily, and ACR50 response and changes from baseline in DAS28-4(ESR) and DAS28-4(CRP) for tofacitinib 10 mg twice daily, baseline BMI was not found to have a clinically significant relationship with selected efficacy outcomes, and there was no clear trend between tofacitinib doses. A sensitivity analysis of stepwise multivariable regression analyses and Lasso regression produced similar results, providing further confirmation of the findings. Together with the descriptive analyses, these results suggest that tofacitinib is an effective treatment option for patients with moderate to severe RA regardless of baseline BMI.

The literature has shown mixed results for efficacy among various advanced therapies based on BMI status. For example, ACR response rates have been reported as

lower, and less radiographic progression has been noted, in sarilumab-treated patients with higher versus lower BMI.^{17–37} Some studies have also shown differences in rates of clinical remission or response to treatments when patients are stratified by BMI.^{17–20} More recently, the impact of BMI on CDAI-defined remission was investigated in patients with RA receiving csDMARDs, primarily MTX, alone or with tocilizumab and, in adjusted analyses, BMI ≥ 30 kg/m² was associated with significantly lower rates of remission than lower BMI categories, regardless of DMARD type.³⁸ Other studies of csDMARDs, TNFi (eg, adalimumab, etanercept and infliximab), and sarilumab have also shown that failure to achieve clinical remission or response to treatment or shorter treatment survival is more likely in patients with obesity versus those with normal BMI.^{17–20,39} The impact of obesity on TNFi may be due to increased levels of circulating TNF, or increased clearance of the drugs.^{40–42} Accordingly, clinical response to the non-TNFi biologic DMARDs abatacept and rituximab does not generally appear to be affected by BMI,^{43,44} although it should be noted that intravenous abatacept is dosed by weight; however, the impact of BMI on the response to tocilizumab is less clear.^{38,45,46}

The impact of tofacitinib based on baseline BMI status has recently been evaluated in other post hoc analyses in patients with active psoriatic arthritis (PsA),⁴⁷ and moderate to severe ulcerative colitis (UC).⁴⁸ Consistent with this analysis, tofacitinib demonstrated greater efficacy than placebo irrespective of baseline BMI. In patients with UC, efficacy was similar regardless of baseline BMI. However, in patients with PsA, reduced efficacy was observed in patients with baseline BMI ≥ 35 kg/m² versus other BMI categories. It should be noted that there are no recommendations to dose-adjust tofacitinib by weight for PsA. Additionally, the analysis of data in patients with PsA included four BMI categories (<25, ≥ 25 to <30, ≥ 30 to <35, and ≥ 35 kg/m²) rather than the three BMI categories used in this analysis.

Limitations of this analysis include that it was performed post hoc, and individual studies were not designed or powered to show differences between baseline BMI categories. Pure placebo data were not available after month 6; further, the placebo data at month 6 were mixed (ie, included patients who switched from placebo at month 3), and therefore, meaningful improvements from baseline may have been observed at month 6 in the placebo group. Additionally, BMI was used as a surrogate for adiposity. The study designs did not include waist circumference measurements which provide a better measure of abdominal obesity, and no metabolic biomarker data (eg, adipokines such as leptin) were collected during the conduct of the phase 3 studies to further support this analysis. Treatment effectiveness was also only assessed in the three common BMI categories (<25, 25 to <30, and ≥ 30 kg/m²) and did not include further analyses for BMI <18.5 or ≥ 35 kg/m².

In addition, some treatments for RA, including TNFi and tocilizumab, are known to affect body composition.⁴⁹ For example, a recent analysis in patients with RA

demonstrated that tocilizumab was associated with significant increases in lean mass without changes in fat mass.⁵⁰ Future research, therefore, could evaluate the effects of tofacitinib on changes in adiposity, lean mass, and fat mass.

In summary, this post hoc analysis demonstrated that the efficacy of tofacitinib was comparable across baseline BMI categories (<25, 25 to <30 and ≥ 30 kg/m²). Tofacitinib resulted in greater improvements in RA outcomes versus placebo, irrespective of baseline BMI category. In general, no clinically meaningful differences were observed, although patients with baseline BMI ≥ 30 kg/m² who received tofacitinib 10 mg twice daily showed higher rates of radiographic non-progression compared with those with baseline BMI <25 kg/m². Overall, BMI was not a consistent affecting factor in either the descriptive or regression analyses. The results of this analysis provide information that will inform clinical decision-making of tofacitinib as a treatment option for adult patients with moderate to severe RA regardless of BMI category, including patients in the obese category (BMI ≥ 30 kg/m²). Further analyses of patients with RA in the real-world setting may provide additional insights into the impact of baseline BMI on the efficacy of tofacitinib.

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Patient consent for publication Not applicable.

Ethics approval This was a post hoc analysis of six randomised controlled studies. All studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation, and were approved by the relevant Institutional Review Board and/or Independent Ethics Committee of the investigational centres. Patients provided written informed consent. No further ethical approval was required for this post hoc analysis.

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Data availability statement Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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