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The impact of body mass index on efficacy and safety in the tofacitinib OCTAVE ulcerative colitis clinical programme

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Summary

Background: Obesity may affect efficacy and safety of biologic treatments for ulcerative colitis (UC). Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of UC.

Aims: To assess efficacy and safety of tofacitinib in patients with UC, by baseline body mass index (BMI).

Methods: This post hoc analysis evaluated patients with UC receiving placebo or tofacitinib from the 8-week OCTAVE Induction 1 and 2 (NCT01465763, NCT01458951) and 52-week OCTAVE Sustain (NCT01458574) studies. Patients were stratified by BMI at OCTAVE Induction 1 and 2 baseline (<25, 25 to <30 and ≥30 kg/m^2). Outcomes included remission, endoscopic improvement, clinical response, sustained steroid-free remission, Inflammatory Bowel Disease Questionnaire total score and Short Form-36 Health Survey scores. Adverse events were evaluated.

Results: At Week 8 of OCTAVE Induction 1 and 2, and Week 52 of OCTAVE Sustain, higher proportions of patients receiving tofacitinib 5 or 10 mg twice daily (b.d.) achieved clinical response vs placebo, regardless of baseline BMI subgroup (all $P < 0.05$). Proportions of patients achieving efficacy endpoints were generally similar across BMI subgroups; in univariate and multivariate regression analyses, BMI was not a significant predictor (all $P \geq 0.05$; univariate BMI [continuous] odds ratio for remission: 0.98 [95% confidence interval 0.95, 1.02]). There was no consistent trend between BMI and adverse events. Among patients receiving tofacitinib 10 mg b.d. in OCTAVE Induction 1 and 2, serious infections were numerically greater in the BMI ≥30 subgroup (3.2%) vs other subgroups (0.4%). Limitations included small patient numbers in the BMI ≥30 subgroup.

Conclusions: Efficacy and safety of tofacitinib were similar in patients with UC regardless of baseline BMI.

1 | INTRODUCTION

The prevalence of both obesity (defined as body mass index [BMI] ≥30 kg/m^2) and ulcerative colitis (UC) have increased substantially within the past few decades.[1,2] Specifically, between 1980 and 2013, the global prevalence of overweight and obesity in adults rose by 28%,[1] while the estimated prevalence of UC in the Western world is now approximately 0.5%.[2] High BMI has also been associated with an increased risk of treatment failure in patients with UC treated with biologics.[3] Consequently, it is important to understand if BMI is a key parameter that should be considered when making treatment decisions for patients with UC; to do this, more evidence is needed regarding the effect of BMI on the efficacy and safety of advanced therapies for UC.

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of UC. The efficacy and safety of tofacitinib in patients with moderately to severely active UC were demonstrated in two identical, 8-week Phase 3 studies (OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951), a 52-week, Phase 3 maintenance study (OCTAVE Sustain, NCT01458574)[4] and an open-label, long-term extension study (OCTAVE Open, NCT01470612).[5] Pharmacokinetic analysis of tofacitinib demonstrated that an increased body weight resulted in lower peak (C_{max}) and higher trough (C_{min}) plasma concentrations, but as these differences were not considered to be clinically relevant, tofacitinib dose adjustment based on patients' body weight is not recommended.[6] In patients with psoriatic arthritis, efficacy response rates to tofacitinib were generally reduced in patients with baseline BMI ≥35 kg/m^2, compared with patients with lower baseline BMI.[7]

This post hoc analysis aimed to determine if BMI or body weight affects the efficacy or safety of tofacitinib 5 or 10 mg twice daily (b.d.) treatment in patients with moderate to severe UC from the OCTAVE Induction 1 and 2 and OCTAVE Sustain studies.

2 | METHODS

2.1 | Patients and study design

Full details of OCTAVE Induction 1 and 2 and OCTAVE Sustain study designs, inclusion and exclusion criteria, and patient populations have been described previously.[4] Briefly, patients in OCTAVE Induction 1 and 2 were randomised to receive tofacitinib 10 mg b.d. or placebo, with final efficacy assessment at Week 8. Patients who completed OCTAVE Induction 1 and 2 with a clinical response could enter OCTAVE Sustain and were re-randomised to receive tofacitinib 5 mg b.d., tofacitinib 10 mg b.d. or placebo, with final efficacy assessment at Week 52. All patients were required to have failed or be intolerant to glucocorticoids, immunosuppressants or tumour necrosis factor inhibitors (TNFi).

In this post hoc analysis, patients were stratified into one of three subgroups according to their BMI (<25, 25 to <30 and ≥30 kg/m^2) at baseline of OCTAVE Induction 1 and 2. These subgroups were defined using the widely accepted BMI categories of normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (≥30 kg/m^2).[8] Changes in BMI over time among patients in OCTAVE Sustain were assessed from baseline through Week 52. For analysis of efficacy and safety outcomes in OCTAVE Sustain, results were based on patient BMI at baseline of OCTAVE Induction 1 and 2.

2.2 | Efficacy assessments

In OCTAVE Induction 1 and 2, the primary efficacy endpoint was remission (defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0) at Week 8. The key secondary endpoint was endoscopic improvement (defined as mucosal healing in the original OCTAVE protocols; defined as a Mayo endoscopic subscore of 0 or 1) at Week 8. Additional endpoints included clinical response (defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1) and health-related quality of life (HRQoL; assessed using the Inflammatory Bowel Disease Questionnaire [IBDQ] total score and the Short Form 36-item Health Survey [SF-36] Physical Component Summary [PCS] and Mental Component Summary [MCS] scores) at Week 8. The IBDQ assesses 32 items, and total scores range from 32 to 224, with higher scores indicating better HRQoL.[4,9] The SF-36 PCS and MCS scores range from 0 to 100, with higher scores indicating better HRQoL.[10]

Similar efficacy endpoints are reported from OCTAVE Sustain, including the primary efficacy endpoint of remission at Week 52. Key secondary endpoints were endoscopic improvement at Week 52 and sustained steroid-free remission (remission at baseline and at both Weeks 24 and 52, without the administration of glucocorticoids for ≥4 weeks before the assessment) among patients who were in remission at OCTAVE Sustain entry. Additional endpoints included IBDQ total score and SF-36 PCS and MCS scores at Week 52.

2.3 | Safety assessments

Discontinuations and adverse events of special interest, including infections, serious infections, opportunistic infections, herpes zoster, major adverse cardiovascular events (MACE), malignancy (excluding non-melanoma skin cancer [NMSC]) and NMSC were reported through Week 8 for OCTAVE Induction 1 and 2, and through Week 52 for OCTAVE Sustain. A serious infection was defined as an infection meeting the serious adverse event reporting criteria or an infection requiring parenteral antimicrobial therapy. Adverse events were coded using the Medical Dictionary for Regulatory Activities, Version 19.0. Patients were required to discontinue from the study if they had a serious infection.

Adjudication of opportunistic infection, MACE, malignancies (excluding NMSC) and NMSC were based on review by an independent committee.

2.4 | Statistical analyses

BMI was defined as weight/(height),[2] with weight in kilograms and height in metres. All BMI are reported as kg/m^2. Data were pooled for analysis of OCTAVE Induction 1 and 2, and were analysed separately for OCTAVE Sustain.

Chi-squared tests for comparisons vs placebo were conducted for efficacy outcomes, both for OCTAVE Induction 1 and 2 combined and for OCTAVE Sustain. Data show the full analysis set with non-responder imputation. An analysis of variance was used to compare the differences in least squares mean change from baseline for HRQoL outcomes, for both OCTAVE Induction 1 and 2 combined and for OCTAVE Sustain.

Univariate and multivariate regression analyses (based on the observed-case data with no imputation for missing data) were used to evaluate possible associations between BMI (as a continuous or categorical variable) or weight, and efficacy outcomes of remission, endoscopic improvement, clinical response (for OCTAVE Induction 1 and 2 and OCTAVE Sustain) and sustained steroid-free remission (for OCTAVE Sustain only). The following variables were included in the univariate and multivariate analyses: BMI (continuous or categorical), treatment, age, gender, race, prior TNFi treatment, prior TNFi failure, prior glucocorticoid treatment, prior immunosuppressant failure, disease duration, disease extent, smoking status, weight and geographic region. For multivariate regression analysis, a backward selection method was used to identify factors for inclusion in the final model at a 0.05 level of significance. P-values are presented without multiplicity adjustment. For the nominal P-values, a 0.05 level of significance was used. For the binary efficacy endpoints, non-responder imputation was used to account for missing values; that is, patients with missing values were treated as non-responders.

TABLE 1 Demographics, baseline characteristics and BMI stratification for patients in the Phase 3 OCTAVE Induction 1 and 2 and OCTAVE Sustain studies (FAS)

	OCTAVE Induction 1 and 2		OCTAVE Sustain[a]		
	Placebo (N = 234)	Tofacitinib 10 mg b.d. (N = 905)	Placebo (N = 198)	Tofacitinib 5 mg b.d. (N = 198)	Tofacitinib 10 mg b.d. (N = 197)
Female, n (%)	102 (43.6)	369 (40.8)	82 (41.4)	95 (48.0)	87 (44.2)
Race, n (%)					
White	186 (79.5)	726 (80.2)	155 (78.3)	164 (82.8)	153 (77.7)
Asian	28 (12.0)	114 (12.6)	26 (13.1)	23 (11.6)	25 (12.7)
Total Mayo score, mean (SD)	9.0 (1.5)[b]	9.0 (1.4)[c]	3.3 (1.8)[d]	3.3 (1.8)[d]	3.4 (1.8)[d]
Age (years), mean (SD)	41.1 (14.4)	41.2 (13.8)	43.4 (14.0)	41.9 (13.7)	42.9 (14.4)
Height (cm), mean (SD)	171.8 (10.1)	171.7 (9.6)	171.5 (10.0)	170.7 (9.5)	171.0 (9.5)
Weight (kg), mean (SD)	73.0 (16.5)[b]	73.6 (16.8)	76.2 (16.7)[d]	73.4 (17.8)[d]	74.6 (15.1)[d]
BMI (kg/m^2), mean (SD)	24.6 (4.7)[b]	24.9 (5.0)	25.8 (4.9)[d]	25.1 (5.1)[d]	25.5 (4.8)[d]
Corticosteroid use, n (%)	113 (48.3)	412 (45.5)	101 (51.0)	101 (51.0)	87 (44.2)
<15 mg/day[e]	35 (34.3)	122 (32.4)	—	—	—
≥15 mg/day[e]	67 (65.7)	254 (67.6)	—	—	—
Subgroups by BMI (kg/m^2), n (%)[f]					
<25	132 (56.7)[b]	533 (58.9)	107 (54.0)	119 (60.1)	113 (57.4)
25 to <30	68 (29.2)[b]	247 (27.3)	60 (30.3)	56 (28.3)	55 (27.9)
≥30	33 (14.2)[b]	125 (13.8)	31 (15.7)	23 (11.6)	29 (14.7)

All BMI are reported as kg/m^2.

Abbreviations: b.d., twice daily; BMI, body mass index; FAS, full analysis set; N, total number of patients in each treatment group; n, number of patients with characteristic; SD, standard deviation.

[a]Demographics and characteristics, including BMI stratification, are from baseline of OCTAVE Induction 1 and 2 unless stated otherwise.

[b]Placebo N = 233 for proportion calculations.

[c]Tofacitinib 10 mg b.d. N = 903 for proportion calculations.

[d]Week 8 of OCTAVE Induction 1 and 2.

[e]Proportion calculations based on the number of patients receiving corticosteroids at baseline with dose information available: placebo N = 102, tofacitinib 10 mg b.d. N = 376 for OCTAVE Induction 1 and 2. Patients in OCTAVE Sustain were required to taper corticosteroid use, except patients receiving budesonide/beclometasone.

[f]Patient subgroups at baseline of OCTAVE Induction 1 and 2.

3 | RESULTS

3.1 | Patients

Baseline demographics and clinical characteristics were similar for the placebo and tofacitinib groups within OCTAVE Induction 1 and 2, and within OCTAVE Sustain (Table 1).

At baseline of OCTAVE Induction 1 and 2, most patients were white (80%) and the mean age of the patients was 41 years. Of patients receiving corticosteroids at baseline of OCTAVE Induction 1 and 2, most were receiving at least 15 mg/day.

Total Mayo score at baseline was lower for patients in OCTAVE Sustain, indicative of having achieved a clinical response in OCTAVE Induction 1 and 2, as per the OCTAVE Sustain inclusion criteria. In all treatment groups, the majority of patients (54%–60%) had a BMI <25, and 12%–16% of patients had a BMI ≥30, based on OCTAVE Induction 1 and 2 baseline (Table 1).

3.2 | Changes in BMI over time

From baseline to Week 52 of OCTAVE Sustain, BMI increased numerically in the tofacitinib 5 and 10 mg b.d. groups compared with placebo (Table 2). Across all treatment groups, BMI increased from baseline to Week 52. Average BMI increases ranged from 0.4 to 1.1 kg/m^2 over the 52-week period.

3.3 | Efficacy outcomes

3.3.1 | Remission

At Week 8 of OCTAVE Induction 1 and 2, a numerically higher proportion of patients treated with tofacitinib 10 mg b.d. achieved remission vs placebo in all three baseline BMI subgroups; the difference was only statistically significant for the baseline BMI <25 subgroup (treatment difference [Δ] 15.2, $P < 0.0001$) (Figure 1A).

At Week 52 of OCTAVE Sustain in patients who received tofacitinib 5 mg b.d., the baseline BMI 25 to <30 subgroup had the highest proportion of patients in remission and greatest difference compared with placebo (Δ 33.0, $P < 0.0001$) (Figure 1B). In contrast, in the tofacitinib 10 mg b.d. group, the baseline BMI ≥30 subgroup had the highest proportion of patients in remission and greatest difference, compared with placebo (Δ 52.0, $P < 0.0001$).

3.3.2 | Endoscopic improvement

At Week 8 of OCTAVE Induction 1 and 2, the proportion of patients with endoscopic improvement was numerically higher among patients receiving tofacitinib 10 mg b.d. vs placebo for all BMI subgroups (Figure 2A); the difference was statistically significant for the baseline BMI <25 subgroup (Δ 18.1, $P < 0.0001$) and the baseline BMI 25 to <30 subgroup (Δ 13.4, $P < 0.05$).

At Week 52 of OCTAVE Sustain in patients receiving tofacitinib 5 mg b.d., the baseline BMI 25 to <30 subgroup had the highest proportion of patients with endoscopic improvement and difference compared with placebo (Δ 29.6, $P < 0.001$) (Figure 2B). However, in patients who received tofacitinib 10 mg b.d., the baseline BMI ≥30 subgroup had the highest proportion of patients with endoscopic improvement and difference compared with placebo (Δ 52.2, $P < 0.0001$).

3.3.3 | Clinical response

Clinical response was generally similar for all BMI subgroups in patients who received tofacitinib 10 mg b.d. at Week 8 of OCTAVE Induction 1 and 2 (Figure 3A); the difference compared with placebo was highest for the baseline BMI <25 subgroup (Δ 30.3, $P < 0.0001$). At Week 52 of OCTAVE Sustain, the proportion of patients achieving a clinical response was similar for each BMI subgroup in patients who received tofacitinib 5 mg b.d. (Figure 3B); the difference compared with placebo was highest for the baseline BMI ≥30 subgroup (Δ 38.2, $P < 0.05$). In patients who received tofacitinib 10 mg b.d., the baseline BMI ≥30 subgroup had the highest proportion of clinical response and difference, compared with placebo (Δ 66.2, $P < 0.0001$).

**TABLE 2** Change from baseline in BMI over time from baseline through Week 52 of OCTAVE Sustain

Mean change from baseline in BMI (kg/m^2)	Placebo (N = 198)	Tofacitinib 5 mg b.d. (N = 198)	Tofacitinib 10 mg b.d. (N = 197)
Week 4	0.3 (0.6)	0.4 (1.3)	0.4 (0.7)
Week 8	0.1 (0.9)	0.5 (1.7)	0.5 (0.8)
Week 16	0.1 (1.1)	0.8 (1.7)	0.6 (1.0)
Week 24	0.2 (1.2)	0.8 (1.9)	0.7 (1.1)
Week 32	0.3 (1.4)	0.8 (1.4)	1.1 (1.2)
Week 40	0.4 (1.5)	0.9 (1.6)	1.1 (1.4)
Week 52	0.4 (1.6)	0.9 (1.6)	1.1 (1.4)

Data represent mean (SD) of change from baseline in BMI from the baseline of OCTAVE Sustain to Week 52 of OCTAVE Sustain.

Abbreviations: b.d., twice daily; BMI, body mass index; N, total number of patients in each treatment group; SD, standard deviation.

FIGURE 1 Proportion of patients in remission at (A) Week 8 of OCTAVE Induction 1 and 2 and (B) Week 52 of OCTAVE Sustain, by baseline BMI subgroup (FAS, NRI). *$P < 0.05$; ***$P < 0.0001$. All comparisons are with placebo; chi-squared test. Patients were stratified by BMI at baseline of OCTAVE Induction 1 and 2. All BMI are reported as kg/m^2. Remission was defined as a total Mayo score of ≤2 with no individual subscore > 1, and a rectal bleeding subscore of 0. Abbreviations: Δ, treatment difference; b.d., twice daily; BMI, body mass index; FAS, full analysis set; N, total number of patients in each treatment group; n, number of patients with the specified response; NRI, non-responder imputation
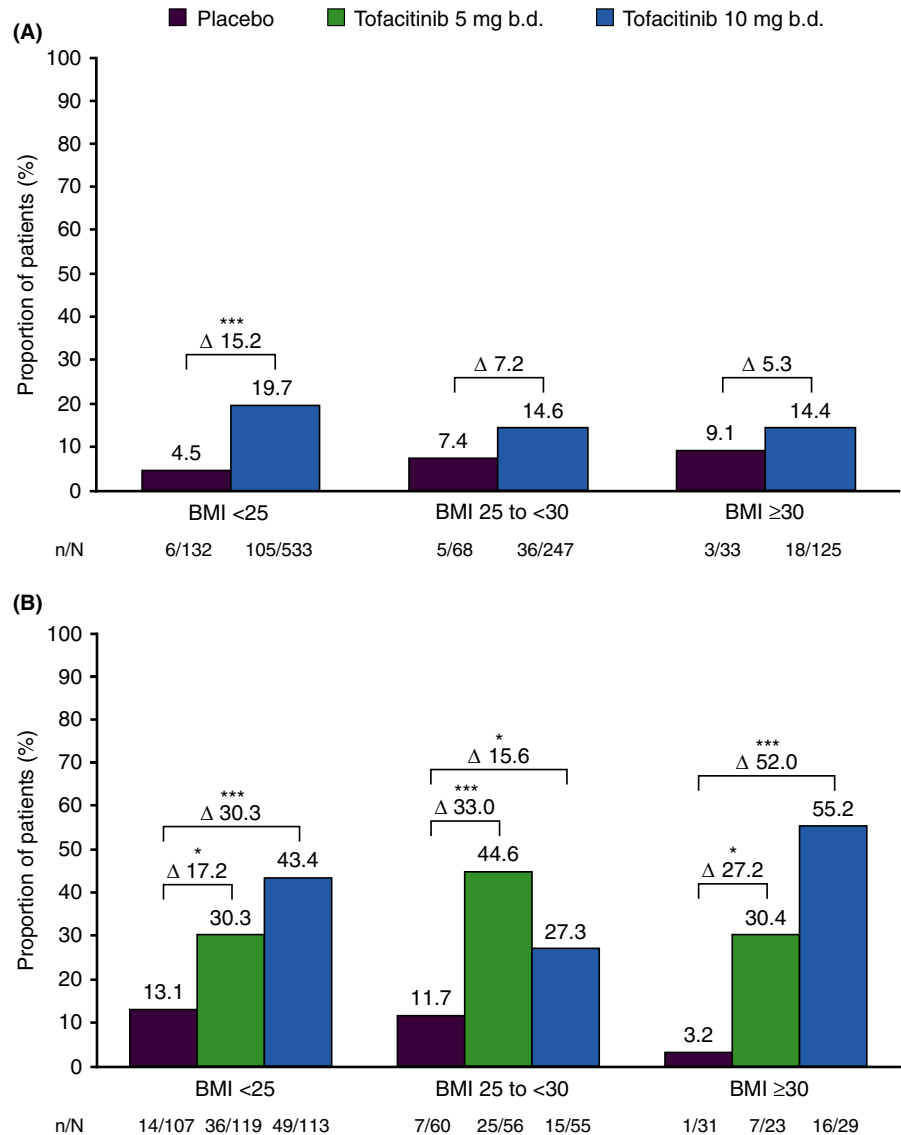
3.3.4 | Sustained steroid-free remission

In OCTAVE Sustain, for both tofacitinib 5 and 10 mg b.d., the baseline BMI ≥30 subgroup had the highest proportion of patients with sustained steroid-free remission at both Week 24 and Week 52 (Figure 4). The greatest differences compared with placebo were observed for the baseline BMI 25 to <30 subgroup for tofacitinib 5 and 10 mg b.d. (Δ 38.9, $P < 0.05$, and Δ 50.0, $P < 0.05$ respectively).

### 3.3.5 | Health-related quality of life

At Week 8 of OCTAVE Induction 1 and 2, all baseline BMI subgroups had significantly greater least squares mean differences from baseline in IBDQ total scores, compared with placebo (all $P < 0.01$, Figure S1a). At Week 52 of OCTAVE Sustain, only the baseline BMI 25 to <30 subgroup, treated with either tofacitinib 5 or 10 mg b.d., experienced additional significant improvements

from baseline in IBDQ total score, compared with placebo ($P < 0.01$; Figure S1b).

At Week 8 in OCTAVE Induction 1 and 2, significant improvements from baseline in SF-36 PCS and MCS scores were reported for all baseline BMI subgroups, compared with placebo, except for the SF-36 MCS score in the baseline BMI ≥30 subgroup (Figure S2a). At Week 52 of OCTAVE Sustain, only the baseline BMI <25 subgroup, treated with either tofacitinib 5 or 10 mg b.d., experienced additional significant improvements from baseline in SF-36 PCS and MCS scores, compared with placebo ($P < 0.05$; Figure S2b).

3.3.6 | Regression analysis for BMI and body weight

In OCTAVE Induction 1 and 2, univariate regression analysis showed that BMI (continuous or categorical) and weight were not significant predictors for the efficacy endpoints of remission, endoscopic improvement, or clinical response at Week 8 ($P ≥ 0.05$ for all) (Table 3); for example: BMI (continuous) odds
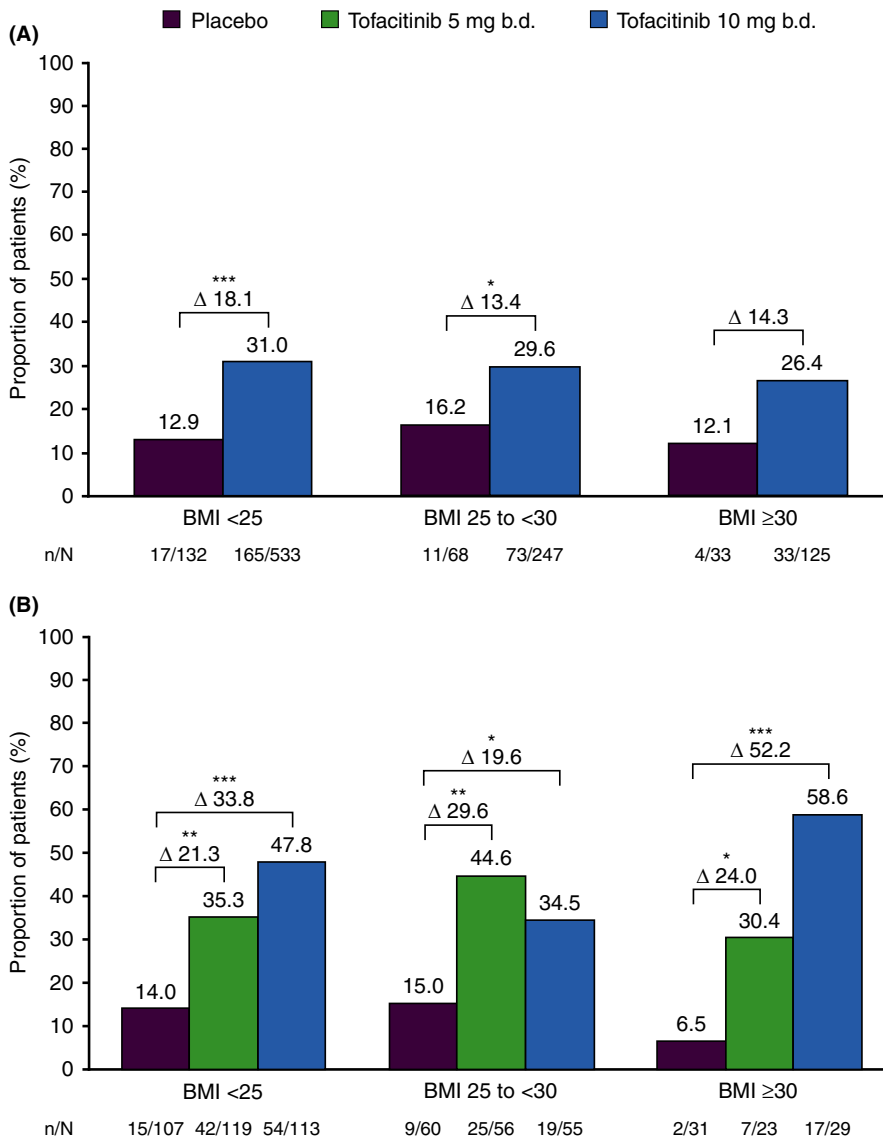
FIGURE 2 Proportion of patients with endoscopic improvement at A) Week 8 of OCTAVE Induction 1 and 2 and B) Week 52 of OCTAVE Sustain, by BMI subgroup (FAS, NRI). *$P < 0.05$; **$P < 0.001$; ***$P < 0.0001$. All comparisons are with placebo; chi-squared test. Patients were stratified by BMI at baseline of OCTAVE Induction 1 and 2. All BMI are reported as kg/m^2. Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1. Abbreviations: Δ, treatment difference; b.d., twice daily; BMI, body mass index; FAS, full analysis set; N, total number of patients in each treatment group; n, number of patients with the specified response; NRI, non-responder imputation

ratio (OR) 0.98 (95% confidence interval [CI] 0.95, 1.02), OR 1.00 (95% CI 0.98, 1.03), and OR 1.02 (95% CI 0.99, 1.05), respectively. Similarly, multivariate logistic analysis for BMI (continuous or categorical) showed that BMI was not a significant predictor for any efficacy endpoint in OCTAVE Induction 1 and 2 ($P > 0.05$). As such, BMI did not meet the selection criteria for inclusion in the final model. However, higher weight was identified as a predictor in the final model for reduced remission (OR 0.99 [95% CI 0.98, 1.00]; $P = 0.0170$).

In OCTAVE Sustain, similar to OCTAVE Induction 1 and 2, univariate regression showed that neither BMI (continuous or categorical) nor weight were significant predictors for any efficacy endpoint at Week 52, including sustained steroid-free remission ($P \geq 0.05$ for all) (Table 3); for example: BMI (continuous) OR 1.01 (95% CI 0.97, 1.05), OR 1.01 (95% CI 0.97, 1.04), OR 1.00 (95% CI 0.96, 1.03) and OR 1.07 (95% CI 0.99, 1.15), respectively.

In the multivariate analysis, BMI (continuous or categorical) was not indicated as a predictor for any efficacy endpoint ($P > 0.05$). However, higher weight was identified as a predictor in the final

model for higher likelihood of sustained steroid-free remission (OR 1.03 [95% CI 1.01, 1.06]; $P = 0.0181$).

3.4 | Safety outcomes

3.4.1 | Discontinuations

In OCTAVE Induction 1 and 2, the highest proportion of discontinuations (all) was in the baseline BMI ≥30 subgroup, for both placebo (n = 4, 12.1%) and tofacitinib 10 mg b.d. (n = 12, 9.6%) (Table 4). The proportions of patients discontinuing due to insufficient clinical response or adverse events were similar among baseline BMI subgroups. In OCTAVE Sustain, the proportions of discontinuations (all) were similar across baseline BMI subgroups for tofacitinib 5 mg b.d., and higher in the baseline BMI <25 and baseline BMI 25 to <30 subgroups for tofacitinib 10 mg b.d. (Table 4). For discontinuation due to insufficient clinical response, proportions were highest in the baseline BMI ≥30 subgroup

FIGURE 3 Proportion of patients with clinical response at A) Week 8 of OCTAVE Induction 1 and 2 and B) Week 52 of OCTAVE Sustain, by BMI subgroup (FAS, NRI). *P < 0.05; **P < 0.001; ***P < 0.0001. All comparisons are with placebo; chi-squared test. Patients were stratified by BMI at baseline of OCTAVE Induction 1 and 2. All BMI are reported as kg/m². Clinical response was defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1. Abbreviations: Δ, treatment difference; b.d., twice daily; BMI, body mass index; FAS, full analysis set; N, total number of patients in each treatment group; n, number of patients with the specified response; NRI, non-responder imputation
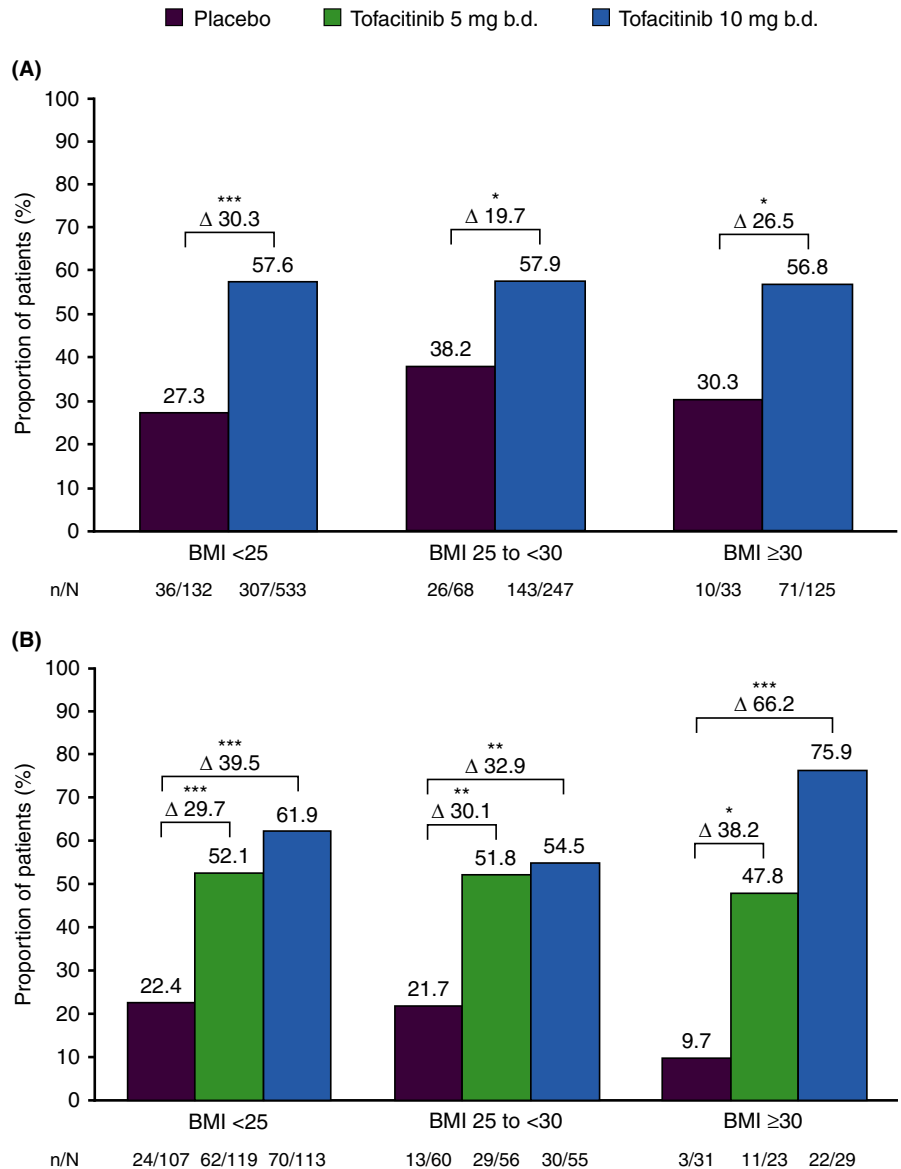
for tofacitinib 5 mg b.d. (n = 10, 43.5%), whereas this subgroup showed the lowest proportions for tofacitinib 10 mg b.d. (n = 1, 3.4%). The proportions of patients discontinuing due to adverse events were highest in the baseline BMI 25 to <30 subgroup for tofacitinib 5 mg b.d. (n = 3, 5.4%) and highest for the baseline BMI 25 to <30 (n = 4, 7.4%) and baseline BMI ≥30 (n = 2, 6.9%) subgroups for tofacitinib 10 mg b.d.

3.4.2 | Infections, serious infections and opportunistic infections

In OCTAVE Induction 1 and 2, for patients receiving tofacitinib 10 mg b.d., the proportion of patients with infections was numerically higher for the baseline BMI 25 to <30 subgroup (n = 62, 25.1%), while the proportion of patients with serious infections was numerically higher for the baseline BMI ≥30 subgroup (n = 4, 3.2%), compared with the other subgroups (Table 4). In OCTAVE

Sustain, similarly for tofacitinib 5 and 10 mg b.d., the proportion of patients with infections was numerically higher for the baseline BMI 25 to <30 subgroup (n = 23, 41.1% and n = 25, 46.3%, respectively) compared with the other subgroups (Table 4), and serious infections were rare among all baseline BMI subgroups for tofacitinib 5 and 10 mg b.d.

For patients receiving tofacitinib 10 mg b.d. in OCTAVE Induction 1 and 2, opportunistic infections were rare, and proportions were similar across baseline BMI subgroups (Table 4). Similarly, in OCTAVE Sustain, there were few opportunistic infections in any treatment group, and proportions of events were similar among baseline BMI subgroups.

3.4.3 | Herpes zoster

In OCTAVE Induction 1 and 2, herpes zoster events (non-serious and serious) were infrequent and numerically similar for patients
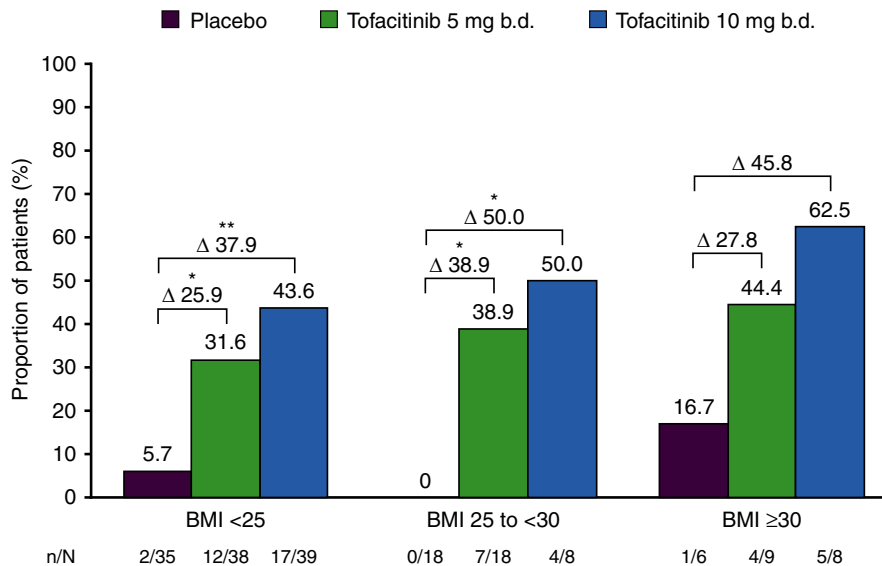
FIGURE 4 Proportion of patients with sustained steroid-free remission in OCTAVE Sustain, by BMI subgroup (FAS, NRI). *$P < 0.05$; **$P < 0.001$. All comparisons are with placebo; chi-squared test. Patients were stratified by BMI at baseline of OCTAVE Induction 1 and 2. All BMI are reported as kg/m^2. Sustained steroid-free remission was defined as being in remission and steroid-free at both Week 24 and Week 52; N was reduced for this outcome compared with other outcomes, as shown. Abbreviations: Δ, treatment difference; b.d., twice daily; BMI, body mass index; FAS, full analysis set; N, total number of patients in each treatment group; n, number of patients with the specified response; NRI, non-responder imputation

TABLE 3 ORs calculated from univariate regression analyses modelling endpoints at Week 8 of OCTAVE Induction 1 and 2 and Week 52 of OCTAVE Sustain

	Remission OR (95% CI) [*P*-value]	Endoscopic improvement OR (95% CI) [*P*-value]	Clinical response OR (95% CI) [*P*-value]	Sustained steroid-free remission OR (95% CI) [*P*-value]
OCTAVE Induction 1 and 2 – all patients (FAS, no imputation)				
Weight	0.99 (0.98, 1.00) [0.067]	1.00 (0.99, 1.01) [0.52]	1.00 (0.99, 1.01) [0.75]	N/A
BMI (continuous)	0.98 (0.95, 1.02) [0.32]	1.00 (0.98, 1.03) [0.90]	1.02 (0.99, 1.05) [0.15]	N/A
BMI (<25 vs ≥30)	1.26 (0.76, 2.10) [0.37]	1.19 (0.78, 1.79) [0.42]	0.95 (0.66, 1.38) [0.80]	N/A
BMI (25 to <30 vs ≥30)	0.91 (0.52, 1.61) [0.75]	1.10 (0.70, 1.73) [0.67]	0.97 (0.65, 1.45) [0.89]	N/A
OCTAVE Sustain – all patients (FAS, no imputation)				
Weight	1.00 (0.99, 1.01) [0.94]	1.00 (0.99, 1.01) [0.95]	1.00 (0.99, 1.01) [0.44]	1.01 (0.99, 1.03) [0.23]
BMI (continuous)	1.01 (0.97, 1.05) [0.59]	1.01 (0.97, 1.04) [0.75]	1.00 (0.96, 1.03) [0.79]	1.07 (0.99, 1.15) [0.077]
BMI (<25 vs ≥30)	0.90 (0.51, 1.57) [0.70]	0.94 (0.54, 1.64) [0.84]	0.96 (0.55, 1.65) [0.87]	0.39 (0.15, 1.06) [0.066]
BMI (25 to <30 vs ≥30)	0.84 (0.46, 1.56) [0.58]	0.89 (0.49, 1.63) [0.71]	0.82 (0.45, 1.49) [0.52]	0.33 (0.11, 1.03) [0.056]

Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; N/A, not applicable; OR, odds ratio.

receiving either placebo or tofacitinib 10 mg b.d. across baseline BMI subgroups (Table 4). In OCTAVE Sustain, herpes zoster events (non-serious and serous) were similar in patients receiving either placebo or tofacitinib 5 mg b.d., with no clear trend across baseline BMI subgroups (Table 4). For patients treated with tofacitinib 10 mg b.d., the percentage of patients who had herpes zoster events (non-serious and serious) was numerically lowest in the baseline BMI <25 subgroup (n = 3, 2.7%) and highest in the baseline BMI ≥30 subgroup (n = 3, 10.3%; Table 4).

3.4.4 | Malignancies and MACE

There were no malignancies (excluding NMSC) for patients receiving tofacitinib in OCTAVE Induction 1 and 2, and MACE were rare (Table 4). For patients receiving tofacitinib 10 mg b.d. in OCTAVE Induction 1 and 2 and OCTAVE Sustain, there were numerically higher proportions of patients with NMSC events in the baseline BMI ≥30 subgroup, compared with other baseline BMI subgroups. Interpretation of these analyses are limited by the small number of

TABLE 4 Discontinuations and safety outcomes of special interest for patients in OCTAVE Induction 1 and 2 and OCTAVE Sustain, stratified by BMI at baseline of OCTAVE Induction 1 and 2 (FAS)

| Subgroups by BMI (kg/m²) | OCTAVE Induction 1 and 2 | | | | | | OCTAVE Sustain | | | | | | | | |
| | Placebo (N = 234) | | | Tofacitinib 10 mg b.d. (N = 905) | | | Placebo (N = 198) | | | Tofacitinib 5 mg b.d. (N = 198) | | | Tofacitinib 10 mg b.d. (N = 197) | | |
	<25	25 to <30	≥30	<25	25 to <30	≥30	<25	25 to <30	≥30	<25	25 to <30	≥30	<25	25 to <30	≥30
Patients evaluated for safety, n (%)	132 (56.4)	68 (29.1)	33 (14.1)	533 (58.9)	247 (27.3)	125 (13.8)	107 (54.0)	60 (30.3)	31 (15.7)	119 (60.1)	56 (28.3)	23 (11.6)	113 (57.4)	54 (27.4)	29 (14.7)
Discontinuation (all), n (%)	10 (7.6)	5 (7.4)	4 (12.1)	39 (7.3)	12 (4.9)	12 (9.6)	78 (72.9)	42 (70.0)	25 (80.7)	51 (42.9)	25 (44.6)	11 (47.8)	41 (36.3)	23 (42.6)	6 (20.7)
Insufficient clinical response[a]	8 (6.1)	3 (4.4)	1 (3.0)	18 (3.4)	6 (2.4)	4 (3.2)	73 (68.2)	37 (61.7)	22 (71.0)	41 (34.5)	19 (33.9)	10 (43.5)	33 (29.2)	19 (35.2)	1 (3.4)
Adverse event[a]	1 (0.8)	1 (1.5)	0 (0.0)	6 (1.1)	3 (1.2)	3 (2.4)	2 (1.9)	0 (0.0)	0 (0.0)	1 (0.8)	3 (5.4)	0 (0.0)	2 (1.8)	4 (7.4)	2 (6.9)
Infection (all), n (%)	13 (9.8)	12 (17.6)	10 (30.3)	99 (18.6)	62 (25.1)	28 (22.4)	25 (23.4)	17 (28.3)	6 (19.4)	43 (36.1)	23 (41.1)	5 (21.7)	41 (36.3)	25 (46.3)	12 (41.4)
Serious infection, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	4 (3.2)	2 (1.9)	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.5)
Opportunistic infection, n (%)[b,c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.8)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	1 (0.9)	2 (3.7)	1 (3.5)
HZ (non-serious and serious), n (%)[b]	0 (0.0)	0 (0.0)	1 (2.6)	4 (0.7)	2 (0.8)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)	3 (2.7)	4 (7.4)	3 (10.3)
MACE, n (%)[b]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Malignancy (excluding NMSC), n (%)[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NMSC, n (%)[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	2 (6.9)

Abbreviations: b.d., twice daily; BMI, body mass index; FAS, full analysis set; HZ, herpes zoster; MACE, major adverse cardiovascular event; N, total number of patients; n, number of patients with event; NMSC, non-melanoma skin cancer; UC, ulcerative colitis.

Patients were stratified by BMI at baseline of OCTAVE Induction 1 and 2. All BMI are reported as kg/m².

[a]Related to study drug. Insufficient clinical response includes patients who discontinued due to the adverse event of worsening UC.

[b]Adjudicated events.

[c]Excludes tuberculosis and herpes zoster with two adjacent dermatomes.

patients in the baseline BMI ≥30 subgroup and the small number of NMSC events.

4 | DISCUSSION

These analyses assessed the efficacy and safety of tofacitinib 5 and 10 mg b.d. in patients with moderate to severe UC, stratified by baseline BMI subgroup. Subgroup analyses did not demonstrate a clear pattern, and showed that patients with a high BMI (≥30) did not experience lower rates of achieving efficacy endpoints, including remission, endoscopic improvement, clinical response and sustained steroid-free remission, compared with other BMI subgroups (<25 or 25 to <30). In OCTAVE Induction 1 and 2, the proportions of patients treated with tofacitinib 10 mg b.d. who achieved the efficacy endpoints at Week 8 were typically consistent for all baseline BMI subgroups. In OCTAVE Sustain, the proportions of patients treated with tofacitinib 10 mg b.d. who achieved efficacy endpoints at Week 52 were typically numerically highest in the baseline BMI ≥30 subgroup, compared with other subgroups. In contrast, patients treated with tofacitinib 5 mg b.d. in the baseline BMI ≥30 subgroup had lower response rates for some efficacy outcomes, compared with other baseline BMI subgroups at Week 52 of OCTAVE Sustain. A higher proportion of patients in OCTAVE Sustain treated with tofacitinib 5 mg b.d. in the baseline BMI ≥30 subgroup discontinued due to insufficient clinical response, compared with patients treated with tofacitinib 10 mg b.d. Further analyses with a larger group of patients are required to understand this observation.

Obesity is recognised as a low-grade chronic inflammatory state[11] through systemic and paracrine increases in levels of cytokines, chemokines and adipokines.[12] Excess adipose tissue increases leptin and resistin secretion, increasing levels of pro-inflammatory cytokines.[13] Therefore, obesity may adversely affect both the inflammatory burden in UC, as well as response to medical therapy.

Previous reports on the efficacy of biologic agents in patients with UC and elevated BMI are inconsistent. It has been previously shown in a meta-analysis of 19 372 patients from 50 studies that obesity is associated with TNFi failure in patients with select immune-mediated inflammatory diseases (eg rheumatoid arthritis and psoriasis/psoriatic arthritis), but not in patients with UC.[14] In contrast, another study in patients with UC (N = 160) suggested that the likelihood of biologic treatment failure increased by approximately 4% with each 1 kg/m^2 increase in BMI.[3] Other data in patients with Crohn's disease suggest that obesity modulates the response to the TNFi infliximab, with earlier flares and shorter time to loss of response in patients with obesity vs patients without obesity.[15,16] In contrast, BMI was found to have no effect on rates of remission among patients with Crohn's disease receiving ustekinumab maintenance therapy.[17] In addition, an analysis of the thiopurines azathioprine and mercaptopurine, which are dosed based on body weight, showed that therapeutic metabolite levels in patients with UC and Crohn's disease were not related to weight or body composition compartments.[18] Together, these findings suggest that further research is required to better understand the impact of obesity on the efficacy of UC treatment and possible consequences of dosing regimens.

Our current report also examined HRQoL using IBDQ total score as well as the SF-36 PCS and MCS scores, stratified by baseline BMI. In OCTAVE Induction 1 and 2, patients in all baseline BMI subgroups treated with tofacitinib 10 mg b.d. experienced significant improvements from baseline in IBDQ total scores at Week 8, compared with placebo, with the BMI ≥30 subgroup having greatest numerical improvement. A similar trend in improvement from baseline was noted in OCTAVE Sustain for both tofacitinib 5 and 10 mg b.d. for SF-36 PCS and MCS scores, compared with placebo. Improvements from baseline in either IBDQ total scores or SF-36 PCS and MCS scores were not significantly different from placebo at Week 52 of OCTAVE Sustain in the highest baseline BMI subgroup (≥30). This may be expected, given that in OCTAVE Sustain patients were required to have achieved a clinical response in OCTAVE Induction 1 or 2, and improvement in HRQoL could also be expected regardless of BMI. However, it has been shown previously that in the general population, elevated BMI was significantly associated with poor HRQoL across all SF-36 domains.[19] Other factors, aside from UC, should be considered when assessing HRQoL in patients with high BMI.

Regression analyses did not identify BMI as a significant predictor for any of the efficacy outcomes studied. Higher body weight was identified as a predictor of remission in OCTAVE Induction 1 and 2 and sustained steroid-free remission in OCTAVE Sustain, although the ORs were small and the clinical significance was uncertain. Although the exact reasons for these findings remain unclear, it has previously been reported that up to two-thirds of patients with inflammatory bowel disease have myopenia, and this has been shown to be independently associated with early treatment failure with TNFi.[20] Patients with myopenia generally have excess fat and less muscle, and therefore can have lower weight and BMI than expected.

Obesity is a known risk factor for reduced response to vaccines and for infection,[21,22] and in OCTAVE Induction 1 and 2 there was a numerically higher rate of serious infections and NMSC in the baseline BMI ≥30 subgroup treated with tofacitinib 10 mg b.d. compared with other baseline BMI subgroups, as well as with placebo. Furthermore, the use of corticosteroids has been linked to increased infection risk,[23] and in OCTAVE Induction 1 and 2 and OCTAVE Sustain, approximately half of patients were receiving corticosteroids at baseline. Otherwise, in general, there was no consistent trend between BMI subgroups and safety events in OCTAVE Induction 1 and 2 or OCTAVE Sustain. However, low patient numbers in the BMI ≥30 subgroup of OCTAVE Sustain, and infrequent serious infection or malignancy events, precluded definitive conclusions. These findings were in line with long-term safety data for tofacitinib in UC up to 4.4 years, which did not identify BMI as a risk factor for serious infections, herpes zoster, opportunistic infections or NMSC in a multivariate risk factor

analysis.[24] Additionally, herpes zoster was the only adverse event more strongly associated with tofacitinib treatment compared with placebo.[24]

This analysis had certain limitations, including an uneven distribution of patients within baseline BMI subgroups, and a low number of patients in the baseline BMI ≥30 subgroup for both the OCTAVE Induction 1 and 2 and OCTAVE Sustain patient populations. This was expected, given that it is generally rare for patients with active inflammatory bowel disease to have a BMI ≥30.[25] In addition, this was a post hoc analysis, and the OCTAVE studies were not powered to evaluate differences between BMI subgroups. Safety events, including serious infections, opportunistic infections and malignancies, were rare in the overall OCTAVE UC clinical programme and for all BMI subgroups in the safety analysis, limiting interpretation of the data. Additionally, as patients were re-randomised at enrolment into OCTAVE Sustain, results from OCTAVE Induction 1 and 2 and OCTAVE Sustain cannot be directly compared. Furthermore, treatment changes following enrolment into OCTAVE Sustain may have contributed to discontinuations due to insufficient clinical response, and hence the relationship to BMI should be interpreted with caution.

In conclusion, this analysis suggested similar efficacy and safety of tofacitinib 5 and 10 mg b.d. in patients with moderate to severe UC, regardless of baseline BMI. As such, dosing adjustments based on weight or BMI are not required for tofacitinib in patients with UC. Further analyses of patients with UC identified from real-world cohorts may provide additional information on the impact of elevated BMI on the efficacy of tofacitinib.

AUTHORSHIP

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Author contributions: Study design: FAF, TQ, PGK, GTM, RM, NL, PPS, DTJ. Performed the research: RM, NL, PPS, DTJ. Collected and analysed the data: RM, NL, PPS, DTJ. Edited and revised the paper: FAF, TQ, PGK, GTM, RM, NL, PPS, DTJ. All authors approved the final version of this article, including the authorship list.

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 anonymised participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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REFERENCES

1. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384:766–781.
2. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46–54.e42.
3. Kurnool S, Nguyen NH, Proudfoot J, et al. High body mass index is associated with increased risk of treatment failure and surgery in biologic-treated patients with ulcerative colitis. *Aliment Pharmacol Ther*. 2018;47:1472–1479.
4. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376:1723–1736.
5. Lichtenstein GR, Loftus EV Jr, Wei SC, et al. DOP61 Tofacitinib, an oral, small-molecule Janus kinase inhibitor, in the treatment of ulcerative colitis: analysis of an open-label, long-term extension study with up to 5.9 years of treatment [abstract]. *J Crohns Colitis*. 2020;14:S100–S101. Abstract DOP61.
6. Pfizer Inc. Xeljanz® (tofacitinib): s of prescribing information. 2020. http://labeling.pfizer.com/ShowLabeling.aspx?id=959. Accessed December 8, 2020
7. Giles JT, Ogdie A, Gomez-Reino JJ, et al. Impact of baseline body mass index on the efficacy and safety of tofacitinib in patients with psoriatic arthritis. *RMD Open*. 2021;7:e001486
8. Centers for Disease Control and Prevention. Defining Adult Obesity. 2020. https://www.cdc.gov/obesity/adult/defining.html. Accessed November 19, 2020
9. Moradkhani A, Beckman LJ, Tabibian JH. Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors. *J Crohns Colitis*. 2013;7:467–473.
10. Coteur G, Feagan B, Keininger DL, Kosinski M. Evaluation of the meaningfulness of health-related quality of life improvements as assessed by the SF-36 and the EQ-5D VAS in patients with active Crohn's disease. *Aliment Pharmacol Ther*. 2009;29:1032–1041.
11. Winer DA, Luck H, Tsai S, Winer S. The intestinal immune system in obesity and insulin resistance. *Cell Metab*. 2016;23:413–426.

12. Singh S, Dulai PS, Zarrinpar A, Ramamoorthy S, Sandborn WJ. Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. *Nat Rev Gastroenterol Hepatol.* 2017;14:110–121.

13. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflamm.* 2013;2013:139239.

14. Singh S, Facciorusso A, Singh AG, et al. Obesity and response to anti-tumor necrosis factor-alpha agents in patients with select immune-mediated inflammatory diseases: a systematic review and meta-analysis. *PLoS One.* 2018;13:e0195123.

15. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2013;19:2118–2124.

16. Guerbau L, Gerard R, Duveau N, et al. Patients with Crohn's disease with high body mass index present more frequent and rapid loss of response to infliximab. *Inflamm Bowel Dis.* 2017;23:1853–1859.

17. Wong ECL, Marshall JK, Reinisch W, Narula N. Body mass index does not impact clinical efficacy of ustekinumab in Crohn's disease: a post hoc analysis of the IM-UNITI trial. *Inflamm Bowel Dis.* 2021;27:848–854.

18. Holt DQ, Strauss BJ, Moore GT. Weight and body composition compartments do not predict therapeutic thiopurine metabolite levels in inflammatory bowel disease. *Clin Transl Gastroenterol.* 2016;7:e199.

19. Corica F, Corsonello A, Apolone G, et al. Construct validity of the Short Form-36 Health Survey and its relationship with BMI in obese outpatients. *Obesity (Silver Spring).* 2006;14:1429–1437.

20. Holt DQ, Varma P, Strauss BJG, Rajadurai AS, Moore GT. Low muscle mass at initiation of anti-TNF therapy for inflammatory bowel disease is associated with early treatment failure: a retrospective analysis. *Eur J Clin Nutr.* 2017;71:773–777.

21. Dobner J, Kaser S. Body mass index and the risk of infection - from underweight to obesity. *Clin Microbiol Infect.* 2018;24:24–28.

22. Painter SD, Ovsyannikova IG, Poland GA. The weight of obesity on the human immune response to vaccination. *Vaccine.* 2015;33:4422–4429.

23. Cross RK. Safety considerations with the use of corticosteroids and biologic therapies in mild-to-moderate ulcerative colitis. *Inflamm Bowel Dis.* 2017;23:1689–1701.

24. Sandborn WJ, Panés J, D'Haens GR, et al. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. *Clin Gastroenterol Hepatol.* 2019;17:1541–1550.

25. Dong J, Chen YI, Tang Y, et al. Body mass index is associated with inflammatory bowel disease: a systematic review and meta-analysis. *PLoS One.* 2015;10:e0144872.

SUPPORTING INFORMATION

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