Tofacitinib as a maintenance therapy in patients with ulcerative colitis stratified by OCTAVE Sustain baseline Mayo endoscopic subscore

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Abstract

Background Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of ulcerative colitis. We evaluated tofacitinib efficacy and safety in the 52-week maintenance study, OCTAVE Sustain, by baseline Mayo endoscopic subscore (MES) following 8-week induction.

Methods The proportion of patients achieving efficacy endpoints at Week 24 or 52 of OCTAVE Sustain was evaluated by baseline MES following 8-week induction. Using logistic regression, the difference in treatment effect (tofacitinib vs. placebo) between baseline MES (0 vs. 1) for each endpoint was assessed. Adverse events were evaluated.

Results At Week 52 of OCTAVE Sustain, a numerically higher proportion of tofacitinib-treated patients achieved remission with OCTAVE Sustain baseline MES of 0 versus 1 (61.9% vs. 36.5% for tofacitinib 5 mg twice daily [BID] and 75.0% vs. 54.2% for tofacitinib 10 mg BID). Similar trends were observed for endoscopic remission and endoscopic improvement. Logistic regression analyses showed a larger treatment effect at Week 52 in patients with baseline MES of 0 versus 1 for clinical response ($p = 0.0306$) in the tofacitinib 5 mg BID group (other endpoints all $p > 0.05$); differences were not significant for any endpoint in the 10 mg BID group (all $p > 0.05$). Infection adverse events were less frequent among patients with baseline MES 0 versus 1.

Conclusions MES may be important in predicting long-term efficacy outcomes for tofacitinib maintenance treatment. Aiming for endoscopic remission during induction with tofacitinib 10 mg BID may allow successful maintenance with tofacitinib 5 mg BID. Safety was consistent with the known tofacitinib safety profile.

Trial registration NCT01458574.

Keywords Efficacy, Tofacitinib, Ulcerative colitis

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Background

Ulcerative colitis (UC) is a chronic disease characterized by relapsing and remitting mucosal inflammation of the rectum and colon [1]. Primary therapeutic goals are the achievement of clinical remission (cessation of rectal bleeding and normalization of bowel habits) and endoscopic improvement (commonly defined as a Mayo endoscopic subscore [MES] of 0 or 1 from a baseline of 2 or 3) [1].

Accumulating evidence indicates that endoscopic improvement is associated with better outcomes, including improved long-term remission rates and a decreased risk of colectomy [2]. However, a general consensus on the optimal MES cut-off (0 or 1) has yet to be determined [3], although the STRIDE initiative recently recommended complete endoscopic healing, defined by a MES of 0, as a treatment goal [4].

Several studies have compared long-term outcomes in patients with UC with endoscopic remission (MES 0) and endoscopic improvement (MES of 0 or 1). Patients with a MES of 0 have been shown to have a reduced risk of disease recurrence [5–7] and better health-related quality of life [8] compared with patients with a MES of 1.

Recent advances in the medical management of UC have made endoscopic improvement a realistic goal [9], and endoscopic indices are increasingly being used as an important measure of therapeutic efficacy in both clinical trials and real-world clinical practice [3]. However, no endoscopic marker has yet been established as an effective prognostic indicator of long-term response to biologic drugs, including tumor necrosis factor inhibitors (TNFi), in patients with UC [10]. The identification of such prognostic markers would help to better select for patients with a high probability of being responders to a particular drug, while minimizing the risks and costs involved for those who will likely be non-responders.

Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of UC. The efficacy and safety of tofacitinib in patients with UC were demonstrated in two phase 3 induction trials (OCTAVE Induction 1 and 2) and a phase 3 maintenance trial (OCTAVE Sustain) [11]. Current guidance recommends using the lowest effective dose for tofacitinib maintenance; therefore, identifying predictors of safe and effective dose reduction of tofacitinib following induction would be beneficial [12, 13]. In this post hoc analysis of data from the OCTAVE Sustain study, we evaluated the efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) maintenance therapy in patients categorized according to baseline MES following 8-week induction therapy and prior TNFi exposure.

Materials and methods

Patients and study design

Full details of the OCTAVE Induction 1 and 2 (ClinicalTrials.gov; NCT01465763 and NCT01458951) and OCTAVE Sustain (ClinicalTrials.gov; NCT01458574) study designs were reported previously [11]. In OCTAVE Induction 1 and 2, patients with moderately to severely active UC, despite previous conventional or TNFi therapy, were randomized to receive tofacitinib induction therapy (10 mg BID) or placebo for 8 weeks. Patients in the tofacitinib or placebo groups who had a clinical response in OCTAVE Induction 1 and 2 (defined as a decrease from induction study baseline total Mayo score of ≥ 3 points and $\geq 30\%$, plus a decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1) were re-randomized to tofacitinib maintenance therapy (5 or 10 mg BID) or placebo for 52 weeks in OCTAVE Sustain. Induction non-responders and patients with loss of response or treatment failure in OCTAVE Sustain were eligible to enroll in an open-label, long-term extension study.

This post hoc analysis included patients in the full analysis set (FAS), defined as patients who received tofacitinib or placebo in OCTAVE Induction 1 and 2 and who were re-randomized to receive tofacitinib or placebo in OCTAVE Sustain, and who had a MES of 0 or 1 (based on central reading of endoscopy) at OCTAVE Sustain baseline (Week 8 of OCTAVE Induction 1 and 2).

The trial protocol for OCTAVE Sustain has previously been published [11] and was registered on ClinicalTrials.gov (NCT01458574) on 25/10/2011. As previously reported, all studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. Study protocols were approved by the Institutional Review Boards and/or independent ethics committees at each of the investigational centers participating in the studies, or a central Institutional Review Board [11]. All the patients provided written informed consent.

Efficacy endpoints

As previously reported, efficacy endpoints at Week 24 or 52 of OCTAVE Sustain (based on central reading of endoscopy) included: remission (defined as a total Mayo score of ≤ 2 with no individual subscore > 1 and a rectal bleeding subscore of 0); endoscopic remission (MES of 0); endoscopic improvement (MES of 0 or 1); clinical response (defined above) [11]. Loss of response was defined by an increase in partial Mayo score of ≥ 2 points from OCTAVE Sustain baseline for two consecutive visits (at least 2 weeks apart), with an increase in rectal bleeding subscore of ≥ 1 from OCTAVE Sustain baseline

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[14]. Treatment failure was defined as an increase from OCTAVE Sustain baseline total Mayo score of ≥ 3 points, plus an increase in rectal bleeding subscore of ≥ 1 point and an increase in MES of ≥ 1 point yielding an absolute MES of ≥ 2, after a minimum of 8 weeks in the study [15].

Safety assessments

Safety assessments included: adverse events (AEs) of special interest (serious infections, opportunistic infections [OIs], and herpes zoster [HZ; non-serious and serious]); gastrointestinal (GI) perforations; malignancies (excluding non-melanoma skin cancer [NMSC]); NMSC; major adverse cardiovascular events (MACE); venous thromboembolism (VTE); infections (all); and deaths. OIs, GI perforations, malignancies (including NMSC), and MACE were reviewed by independent adjudication committees.

Analysis sets

The efficacy analysis set included patients in the FAS with non-missing binary efficacy endpoint responses (observed data). The time-to-event analysis set included all patients in the FAS (observed data). The safety analysis set included patients who received at least one dose of study medication in OCTAVE Sustain.

Statistical analyses

The proportion of patients who achieved binary efficacy endpoints at Week 24 or 52 of OCTAVE Sustain was evaluated descriptively according to treatment group (tofacitinib 5 or 10 mg BID or placebo), OCTAVE Sustain baseline MES (0 vs. 1), and prior TNFi therapy.

In addition, the difference in treatment effect between baseline OCTAVE Sustain MES subgroups (0 vs. 1) was assessed using a logistic regression model, which included prior TNFi exposure status, treatment allocation, baseline MES, and treatment by baseline MES interaction. These analyses tested the null hypothesis that the tofacitinib 5 or 10 mg BID versus placebo difference (treatment effect) was the same for patients with a baseline MES of 0 as it was for those with a MES of 1.

Cox proportional hazards regression was used to model the difference in treatment effect between baseline MES (0 vs. 1) for time to treatment failure and time to loss of response. The model included prior TNFi exposure status, treatment allocation, baseline MES, and treatment by baseline MES interaction. These analyses tested whether the difference in the risk of the event between tofacitinib 5 or 10 mg BID and placebo was the same for patients with a baseline MES of 0 as it was for those with a baseline MES of 1.

Incidence rates, defined as the number of unique patients with events per 100 patient-years of exposure, were evaluated for AEs of special interest, which were counted up to 28 days beyond the last dose of study treatment. Confidence intervals (CIs) were calculated according to the Exact Poisson method, adjusted for patient-years.

Results

Patients

A total of 255 patients were included in the efficacy analysis set (patients in the FAS with non-missing binary efficacy endpoint responses [observed data]; tofacitinib 5 mg BID, n = 95; tofacitinib 10 mg BID, n = 75; placebo, n = 85). Prior TNFi exposure across the treatment groups among these 255 patients was 37.9% (36/95), 38.7% (29/75), and 45.9% (39/85), respectively. The time-to-event analysis set included a total of 295 patients (all patients in the FAS; tofacitinib 5 mg BID, n = 105; tofacitinib 10 mg BID, n = 89; placebo, n = 101). The safety analysis set included 294 patients who received at least one dose of study medication in OCTAVE Sustain (tofacitinib 5 mg BID, n = 105; tofacitinib 10 mg BID, n = 88; placebo, n = 101). Detailed baseline demographics and clinical characteristics of patients in OCTAVE Sustain were reported previously [11].

Demographics and baseline characteristics among all patients with OCTAVE Sustain baseline MES of 0 or 1 were generally similar between treatment groups and subgroups stratified by baseline MES, except for the proportion of patients in remission, total Mayo score, and the proportion of patients receiving corticosteroids at baseline of OCTAVE Sustain (Table 1). Across all treatment groups, the proportion of patients in remission was higher in patients with a baseline MES of 0 (80.0–88.5%) than in patients with a baseline MES of 1 (48.0–56.6%). Total Mayo score was lower in patients with a baseline MES of 0 versus 1 (0.9–1.5 vs. 2.4–2.7, respectively).

Across all treatment groups in OCTAVE Sustain, there were similar proportions of patients with a baseline MES of 0 (tofacitinib 5 mg BID, 21.0%; tofacitinib 10 mg BID, 22.5%; placebo, 25.7%).

Efficacy endpoints at Week 24 or Week 52 of OCTAVE Sustain

Overall, the proportion of patients who met efficacy endpoints was higher with tofacitinib than with placebo, regardless of tofacitinib dose or baseline MES. In general, the proportion of patients treated with tofacitinib who achieved efficacy endpoints at Week 52 was numerically higher for patients with a baseline MES of 0 than for those with a MES of 1. This was observed for remission, endoscopic remission, and endoscopic improvement, regardless

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of dose or prior TNFi exposure status (Fig. 1). For clinical response, the proportion was numerically higher for patients with a baseline MES of 0 versus 1 in the tofacitinib 5 mg BID group, but not in the tofacitinib 10 mg BID group. A numerically higher proportion of tofacitinib-treated patients achieved remission with a baseline MES of 0 versus 1 at Week 52 of OCTAVE Sustain (61.9% vs. 36.5% for tofacitinib 5 mg BID and 75.0% vs. 54.2% for tofacitinib 10 mg BID, respectively). However, at Week 24 this trend was only evident in the tofacitinib 5 mg BID group; the proportion of tofacitinib-treated patients who achieved remission at Week 24 with a baseline MES of 0 versus 1 was 76.2% versus 38.7% for tofacitinib 5 mg BID and 55.6% versus 58.5% for tofacitinib 10 mg BID, respectively. A similar trend of a higher proportion of tofacitinib-treated patients in remission at Week 52 with a baseline MES of 0 versus 1 was also observed irrespective of remission status at baseline of OCTAVE Sustain, although data were limited by small patient numbers in some groups (Fig. 2).

Logistic regression analyses of clinical response at Week 52 showed a significantly larger tofacitinib versus placebo treatment effect for patients with a baseline MES of 0 versus 1 in the tofacitinib 5 mg BID group (odds ratio [OR] [95% CI] 7.41 [1.21–45.52]; $p = 0.0306$) but not in the tofacitinib 10 mg BID group (OR 1.56 [0.24–10.33]; $p = 0.6419$). The difference in the tofacitinib 5 mg BID treatment effect between baseline MES of 0 and 1 was not evident for remission (OR 3.29 [0.58–18.70]; $p = 0.1790$), endoscopic remission (OR 1.51 [0.10–22.67]; $p = 0.7655$), or endoscopic improvement (OR 3.38 [0.59–19.40]; $p = 0.1720$). Similarly, the treatment effect of tofacitinib 10 mg BID was not significantly different between baseline MES 0 and 1 for any efficacy endpoint: remission, OR 3.00 (0.45–19.86); $p = 0.2546$; endoscopic remission, OR

Table 1 Baseline demographic and clinical characteristics by treatment group and baseline MES

Variable	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Placebo	
	MES = 0 (N = 22)	MES = 1 (N = 83)	MES = 0 (N = 20)	MES = 1 (N = 69)	MES = 0 (N = 26)	MES = 1 (N = 75)
Age (years), mean (SD)	36.5 (11.6)	41.9 (13.3)	39.5 (13.9)	42.0 (15.9)	42.3 (13.6)	43.4 (14.0)
Gender (female), n (%)	12 (54.5)	44 (53.0)	12 (60.0)	30 (43.5)	8 (30.8)	32 (42.7)
Race, n (%)						
White	17 (77.3)	72 (86.7)	13 (65.0)	51 (73.9)	21 (80.8)	63 (84.0)
Asian	3 (13.6)	7 (8.4)	4 (20.0)	11 (15.9)	2 (7.7)	7 (9.3)
Weight (kg), mean (SD)	79.1 (21.3)	72.9 (18.7)	71.9 (17.0)	72.0 (13.4)	76.0 (13.8)	77.7 (15.4)
BMI (kg/m²), mean (SD)	27.0 (7.1)	24.9 (5.0)	25.8 (5.3)	24.6 (4.0)	25.4 (5.1)	26.2 (4.7)
Remission at baseline, n (%)[a]	18 (81.8)	47 (56.6)	16 (80.0)	39 (56.5)	23 (88.5)	36 (48.0)
Total Mayo score at baseline, mean (SD)[a]	1.5 (1.3)	2.4 (1.2)	1.1 (1.0)	2.4 (1.1)	0.9 (1.2)	2.7 (1.4)
Corticosteroid use at baseline, n (%)[a]	8 (36.4)	53 (63.9)	11 (55.0)	27 (39.1)	13 (50.0)	37 (49.3)
5-ASA use at baseline, n (%)[a]	18 (81.8)	66 (79.5)	16 (80.0)	53 (76.8)	18 (69.2)	60 (80.0)
Prior TNFi exposure, n (%)[b]	7 (31.8)	33 (39.8)	6 (30.0)	29 (42.0)	8 (30.8)	38 (50.7)
Prior TNFi failure, n (%)[b]	4 (18.2)	30 (36.1)	5 (25.0)	27 (39.1)	8 (30.8)	36 (48.0)
Prior immunosuppressant failure, n (%)[b]	15 (68.2)	60 (72.3)	11 (55.0)	51 (73.9)	15 (57.7)	42 (56.0)
Extent of disease, n (%)[b]						
Proctosigmoiditis	4 (18.2)	16 (19.5)	5 (25.0)	10 (14.5)	2 (7.7)	11 (14.7)
Left-sided colitis	5 (22.7)	31 (37.8)	9 (45.0)	22 (31.9)	12 (46.2)	23 (30.7)
Extensive colitis/pancolitis	13 (59.1)	35 (42.7)	6 (30.0)	37 (53.6)	12 (46.2)	40 (53.3)
Proctitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)

MES, based on central read of endoscopy, was assessed at Week 8 of OCTAVE Induction 1 or 2 (baseline of OCTAVE Sustain)

5-ASA 5-aminosalicylates; *BID* Twice daily; *BMI* Body mass index; *MES* Mayo endoscopic subscore; *N* Number of evaluable patients in the treatment group and MES subgroup; *n* Number of patients within the given category; *SD* Standard deviation; *TNFi* Tumor necrosis factor inhibitor

[a] Data from baseline of OCTAVE Sustain

[b] Data from baseline of OCTAVE Induction 1 or 2

3.94 (0.25–60.81); $p = 0.3265$; or endoscopic improvement, OR 2.08 (0.31–13.81); $p = 0.4475$.

We next examined the proportion of patients achieving efficacy endpoints at Week 52 of OCTAVE Sustain based on the extent of change in MES from baseline to Week 8 of OCTAVE Induction 1 or 2 (Fig. 3). The proportion of tofacitinib-treated patients achieving efficacy endpoints in OCTAVE Sustain was similar for patients with a 1-point or 2-point change in MES from baseline to Week 8 of OCTAVE Induction 1 or 2, although there was a general trend for the proportion of patients meeting each endpoint to be slightly higher in patients with a 2-point change versus those who had a 1-point change. Data for patients with a 3-point change in MES from baseline to Week 8 of OCTAVE Induction 1 or 2 were limited by small patient numbers.

For patients treated with tofacitinib 5 mg BID, Cox proportional hazards regression showed that the relative risk (tofacitinib vs. placebo) of treatment failure or loss of response was significantly lower for patients with a baseline MES 0 versus 1 (hazard ratio [95% CI] for MES 0 vs. 1: 0.29 [0.10–0.84]; $p = 0.0231$ for treatment failure and 0.26 [0.08–0.81]; $p = 0.0209$ for loss of response) (Fig. 4). In contrast, for patients treated with tofacitinib 10 mg BID, the risk versus placebo was not significantly different between baseline MES 0 versus 1 for treatment failure or loss of response (Fig. 4).

Safety

Among patients receiving tofacitinib 5 mg BID in OCTAVE Sustain, a lower proportion of patients with a baseline MES of 0 versus 1 had infection AEs (all) (22.7% vs. 45.8%). This trend was weaker in the placebo group (19.2% vs. 29.3%) and among patients receiving tofacitinib 10 mg BID (35.0% vs. 39.7%). AEs of special interest are summarized in Table 2. The proportions of patients with OIs or HZ (non-serious and serious) were low across treatment and MES subgroups. No cases of serious infection, malignancy (including NMSC), MACE, GI perforation, or VTE (including deep vein thrombosis and/or pulmonary embolism) were reported in either tofacitinib treatment group. No deaths were reported in any treatment group.

Discussion

In this post hoc analysis of data from the phase 3 OCTAVE Sustain study, we examined the efficacy and safety of tofacitinib maintenance therapy in patients categorized according to OCTAVE Sustain baseline MES to determine whether a MES of 0 (endoscopic remission) following 8-week induction therapy is associated with superior long-term outcomes at 52 weeks compared with a MES of 1 in patients with moderate-to-severe UC.

In general, a numerically higher proportion of tofacitinib-treated patients with a baseline MES of 0 at the start of maintenance therapy achieved efficacy endpoints at Week 52 compared to patients with a baseline MES of 1. This trend was observed regardless of prior TNFi exposure status or remission status at baseline of OCTAVE Sustain. When the proportion of patients achieving efficacy endpoints at Week 52 was stratified by change in MES from baseline to Week 8 of OCTAVE Induction 1 or 2, there was a slight trend for values to be numerically higher in patients who had a 2-point reduction in MES compared with those who had a 1-point reduction in MES. These results are broadly consistent with those of previous studies, which showed that patients with a MES of 0 have better outcomes compared with patients with a MES of 1, including a reduced risk of disease recurrence [5–7, 16], a higher rate of clinical remission [17], and better health-related quality of life [8].

In the tofacitinib 5 mg BID group, Week 52 results for clinical response showed a significant difference in the tofacitinib treatment effect for a baseline MES of 0 versus 1; however, this difference was not significant for remission, endoscopic remission, or endoscopic improvement in the 5 mg BID group or for any endpoint in the 10 mg BID group. This lack of statistical significance could at least in part be due to the small sample sizes, as a numerical trend was observed for most endpoints. In addition, for the tofacitinib 5 mg BID group, the difference in risk of treatment failure and loss of response versus placebo was significantly larger in patients with a baseline MES of 0 compared with those with a MES of 1. These differences were also not seen in the tofacitinib 10 mg BID group. These results suggest that remaining on the induction dose of tofacitinib 10 mg BID until endoscopic remission (MES of 0) is achieved may improve the probability of

(See figure on next page.)
Fig. 1 Proportion of patients achieving efficacy endpoints[a] by baseline MES, overall and by prior TNFi exposure. MES, based on central read of endoscopy, was assessed at Week 8 of OCTAVE Induction 1 or 2 (baseline of OCTAVE Sustain). Only patients who had a MES of 0 or 1 at Week 8 of OCTAVE Induction 1 or 2 are included in this analysis. [a]At Week 52 of OCTAVE Sustain (FAS, observed data). BID, twice daily; MES, Mayo endoscopic subscore; FAS, full analysis set; n, number of patients meeting the endpoint criteria; N1, number of patients in each subgroup with non-missing data; TNFi, tumor necrosis factor inhibitor
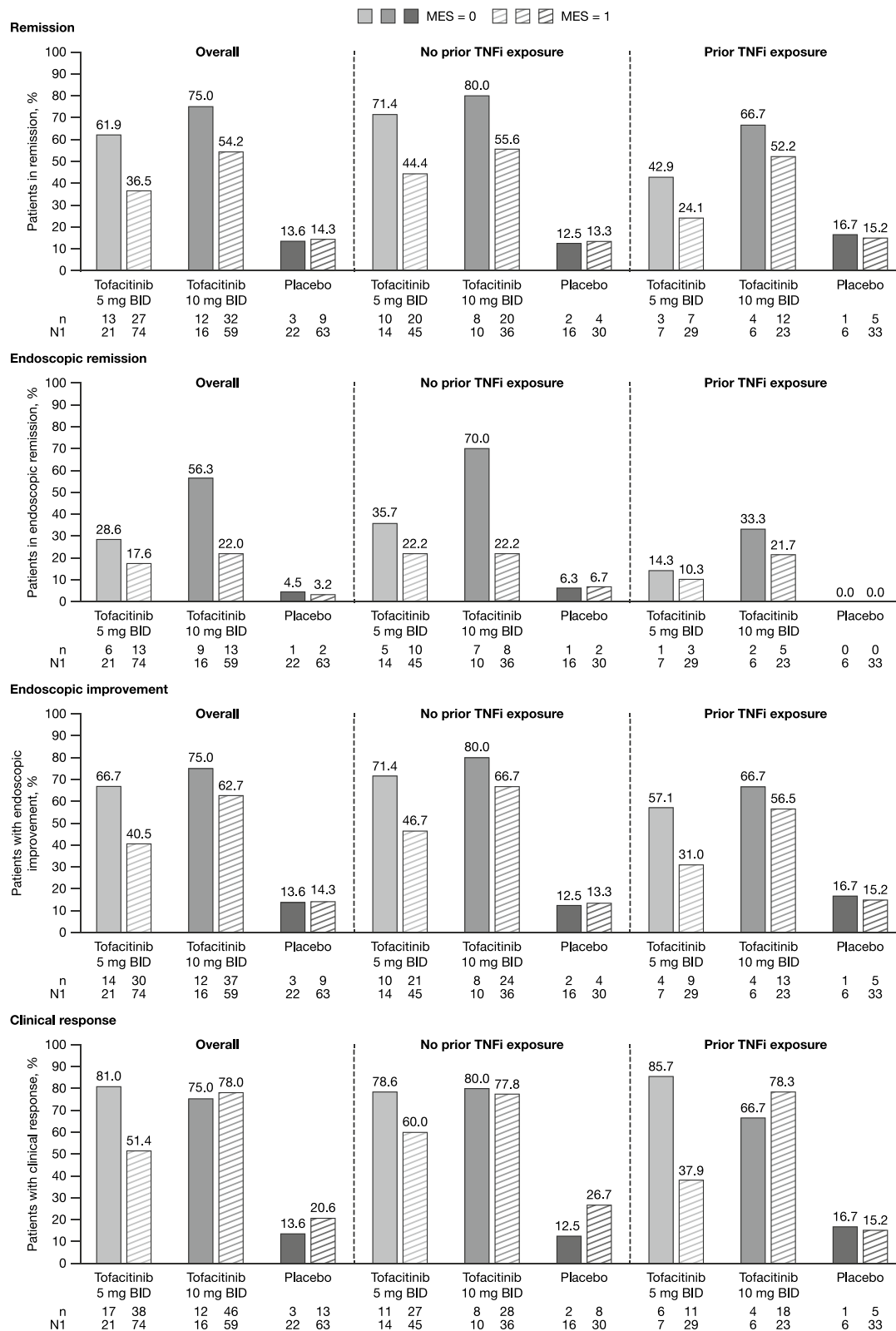
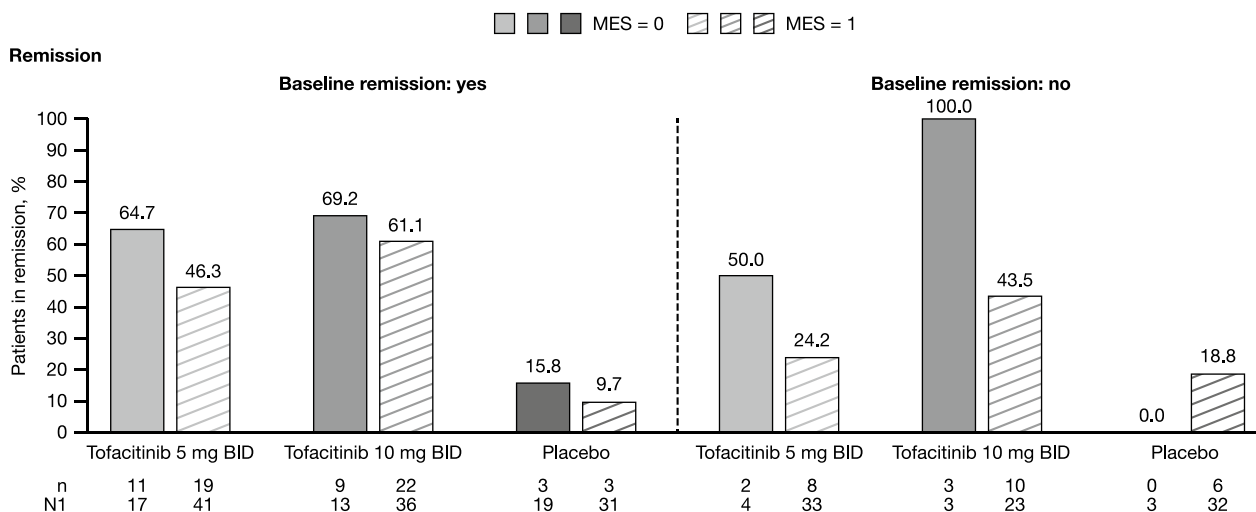**Fig. 1** (See legend on previous page.)

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Fig. 2 Proportion of patients in remission[a] by baseline remission status, and baseline MES. MES, based on central read of endoscopy, was assessed at Week 8 of OCTAVE Induction 1 or 2 (baseline of OCTAVE Sustain). Only patients who had a MES of 0 or 1 at Week 8 of OCTAVE Induction 1 or 2 are included in this analysis. [a]At Week 52 of OCTAVE Sustain (FAS, observed data). BID, twice daily; FAS, full analysis set; MES, Mayo endoscopic subscore; n, number of patients meeting the endpoint criteria; N1, number of patients in each treatment group with non-missing data

long-term efficacy with the 5 mg BID maintenance dose. This predictor of safe and effective dose reduction is particularly beneficial as current guidance recommends using the lowest effective dose for tofacitinib maintenance [12, 13].

Safety outcomes were consistent with the known safety profile of tofacitinib in UC, irrespective of baseline MES status. However, among patients receiving tofacitinib 5 mg BID, a lower proportion of patients with a baseline MES of 0 had infection AEs, compared with patients with a MES of 1. This trend was weaker but present in the tofacitinib 10 mg BID and placebo groups. This may suggest that patients with inflammatory burden, as suggested by a MES of 1, may be more susceptible to infection than those with a MES of 0 [18, 19]. However, this finding was based on a relatively small sample size and should be interpreted with caution.

Noted limitations of this analysis include the post hoc exploratory nature of the analyses and the small sample size, particularly of the TNFi exposure subgroups. Another limitation of these analyses is that the population of patients in the tofacitinib UC program may not be fully representative of the global UC population. It should

also be noted that differences in baseline corticosteroid use between treatment groups and MES subgroups may have contributed to the observed trends for the tofacitinib 10 and 5 mg BID groups.

Additionally, inherent limitations of the MES include the lack of validation, the inability to distinguish superficial ulcers from deep ulcers, and the fact that the score only evaluates the most severely affected visualized segment, with no minimal insertion length. The MES is also limited by subjectivity and potential operator variability, although central reading was employed in this study to minimize any potential bias. While confirmation of remission status via histological assessment would further improve the reliability of these results, histological data were not collected in the OCTAVE clinical programme as these studies pre-dated the current FDA guidance on the inclusion of a histological assessment as an exploratory endpoint.

In conclusion, these analyses suggest that MES at the end of induction therapy may be an important factor in predicting long-term efficacy outcomes following maintenance treatment with tofacitinib. Aiming for endoscopic remission during induction with tofacitinib

(See figure on next page.)
Fig. 3 Proportion of patients achieving efficacy endpoints[a] by reduction in MES[b] during 8-week induction. MES, based on central read of endoscopy, was assessed at baseline and Week 8 of OCTAVE Induction 1 or 2. Only patients who had a MES of 0 or 1 at Week 8 of OCTAVE Induction 1 or 2 are included in this analysis. [a]At Week 52 of OCTAVE Sustain (FAS, observed data). [b]From baseline to Week 8 of OCTAVE Induction 1 or 2. BID, twice daily; MES, Mayo endoscopic subscore; FAS, full analysis set; n, number of patients meeting the endpoint criteria; N1, number of patients in each subgroup with non-missing data
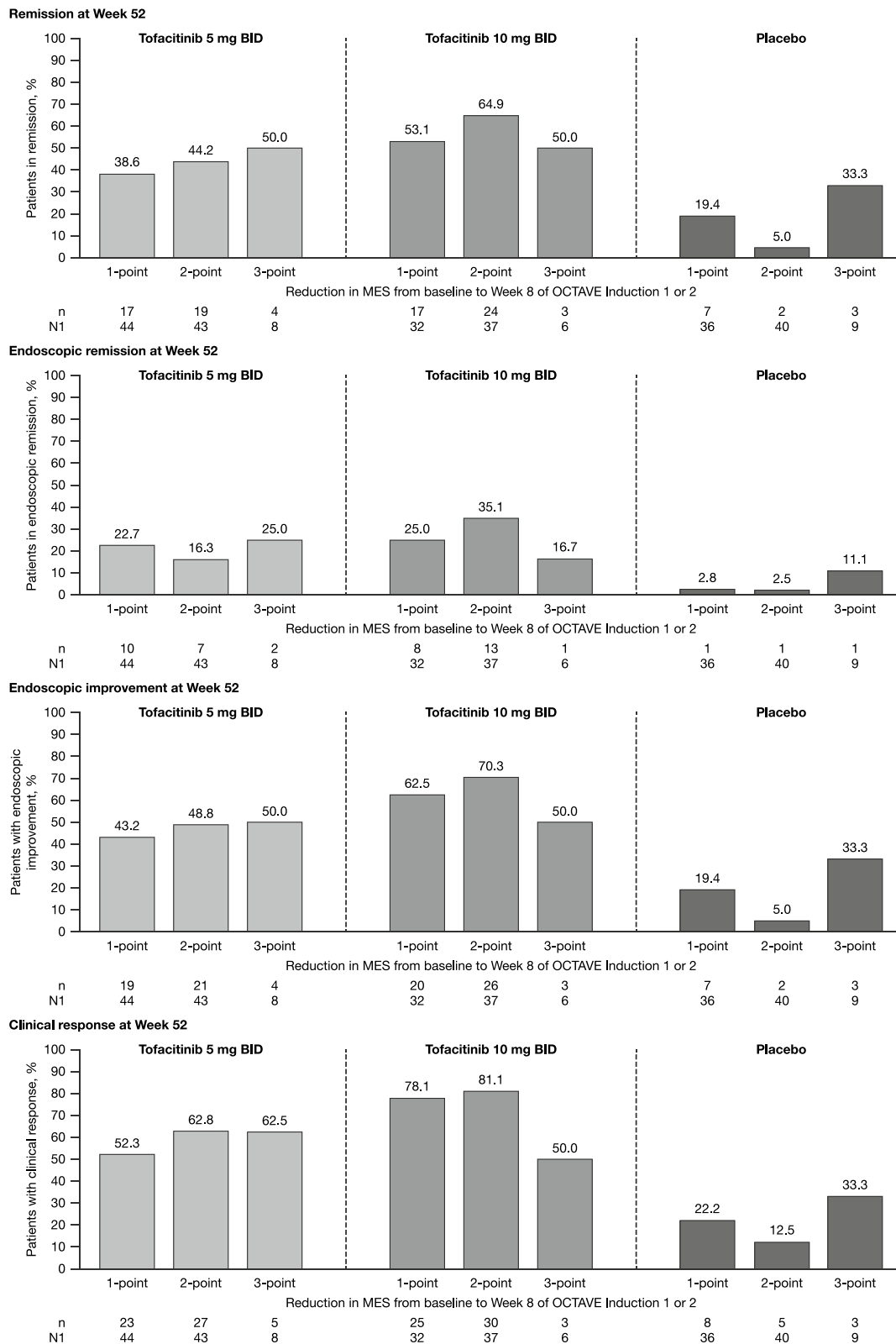
Remission at Week 52

	Tofacitinib 5 mg BID			**Tofacitinib 10 mg BID**			**Placebo**		
	1-point	2-point	3-point	1-point	2-point	3-point	1-point	2-point	3-point
n	17	19	4	17	24	3	7	2	3
N1	44	43	8	32	37	6	36	40	9

Remission values: 5 mg BID — 1-point 38.6, 2-point 44.2, 3-point 50.0; 10 mg BID — 1-point 53.1, 2-point 64.9, 3-point 50.0; Placebo — 1-point 19.4, 2-point 5.0, 3-point 33.3.

Endoscopic remission at Week 52

	Tofacitinib 5 mg BID			**Tofacitinib 10 mg BID**			**Placebo**		
	1-point	2-point	3-point	1-point	2-point	3-point	1-point	2-point	3-point
n	10	7	2	8	13	1	1	1	1
N1	44	43	8	32	37	6	36	40	9

Endoscopic remission values: 5 mg BID — 1-point 22.7, 2-point 16.3, 3-point 25.0; 10 mg BID — 1-point 25.0, 2-point 35.1, 3-point 16.7; Placebo — 1-point 2.8, 2-point 2.5, 3-point 11.1.

Endoscopic improvement at Week 52

	Tofacitinib 5 mg BID			**Tofacitinib 10 mg BID**			**Placebo**		
	1-point	2-point	3-point	1-point	2-point	3-point	1-point	2-point	3-point
n	19	21	4	20	26	3	7	2	3
N1	44	43	8	32	37	6	36	40	9

Endoscopic improvement values: 5 mg BID — 1-point 43.2, 2-point 48.8, 3-point 50.0; 10 mg BID — 1-point 62.5, 2-point 70.3, 3-point 50.0; Placebo — 1-point 19.4, 2-point 5.0, 3-point 33.3.

Clinical response at Week 52

	Tofacitinib 5 mg BID			**Tofacitinib 10 mg BID**			**Placebo**		
	1-point	2-point	3-point	1-point	2-point	3-point	1-point	2-point	3-point
n	23	27	5	25	30	3	8	5	3
N1	44	43	8	32	37	6	36	40	9

Clinical response values: 5 mg BID — 1-point 52.3, 2-point 62.8, 3-point 62.5; 10 mg BID — 1-point 78.1, 2-point 81.1, 3-point 50.0; Placebo — 1-point 22.2, 2-point 12.5, 3-point 33.3.

All charts: x-axis "Reduction in MES from baseline to Week 8 of OCTAVE Induction 1 or 2".

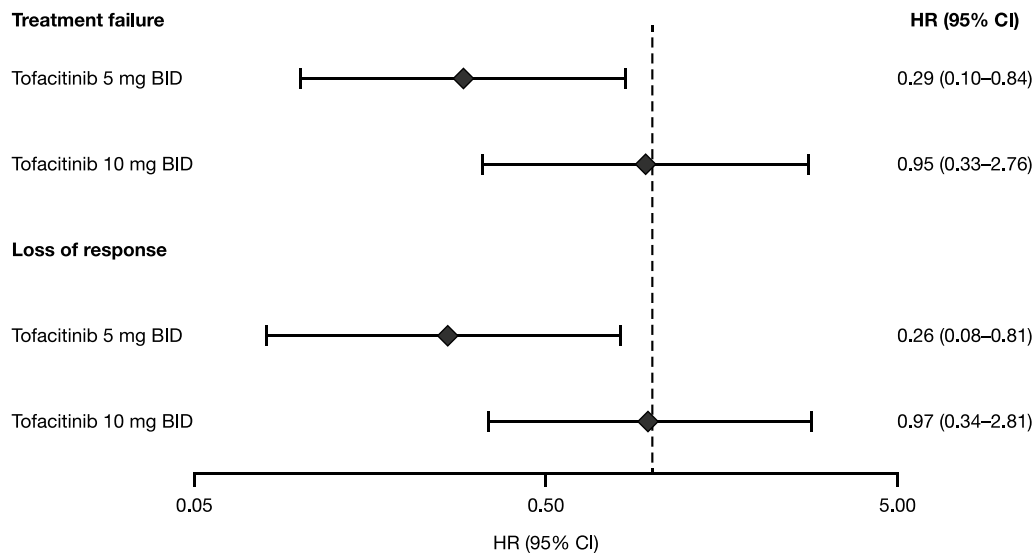**Fig. 3** (See legend on previous page.)

Fig. 4 Cox proportional hazards regression[a] modeling risk versus placebo according to baseline[b] MES (0 vs. 1). Data represent the time-to-event analysis set (patients in the FAS with OCTAVE Sustain baseline MES of 0 or 1; observed data), which included a total of 295 patients (tofacitinib 5 mg BID, n = 105; tofacitinib 10 mg BID, n = 89; placebo, n = 101). [a]Cox proportional hazards regression was used to model the difference in treatment effect (tofacitinib vs. placebo risk) between baseline MES (0 vs. 1) for time to treatment failure and time to loss of response. The model included prior TNFi exposure status, treatment allocation, baseline MES, and treatment by baseline MES interaction. [b]Baseline of OCTAVE Sustain. BID, twice daily; CI, confidence interval; FAS, full analysis set; HR, hazard ratio, MES, Mayo endoscopic subscore; n, number of patients in each treatment group; TNFi, tumor necrosis factor inhibitor

Table 2 Summary of AEs of special interest by treatment group and baseline MES

	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Placebo	
	MES = 0 (N = 22)	MES = 1 (N = 83)	MES = 0 (N = 20)	MES = 1 (N = 68)	MES = 0 (N = 26)	MES = 1 (N = 75)
Serious infections, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)
IR (95% CI)	0 (0–18.9)	0 (0–6.0)	0 (0–22.7)	0 (0–6.3)	0 (0–27.2)	2.4 (0.1–13.1)
Opportunistic infections, n (%)[a,b]	0 (0)	1 (1.2)	1 (5.0)	1 (1.5)	0 (0	0 (0)
IR (95% CI)	0 (0–18.9)	1.7 (0.0–9.2)	6.6 (0.2–36.5)	1.8 (0.0–9.7)	0 (0–27.2)	0 (0–8.7)
HZ (non-serious and serious), n (%)	0 (0)	2 (2.4)	2 (10.0)	2 (2.9)	0 (0)	0 (0)
IR (95% CI)	0 (0–18.9)	3.4 (0.4–12.1)	14.0 (1.7–50.6)	3.5 (0.4–12.7)	0 (0–27.2)	0 (0–8.7)
GI perforations, n (%)[a,c]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)
IR (95% CI)	0 (0–18.9)	0 (0–6.0)	0 (0–22.7)	0 (0–6.3)	0 (0–27.2)	2.4 (0.1–13.1)
Malignancies (excl. NMSC), n (%)[a]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)
IR (95% CI)	0 (0–18.9)	0 (0–6.0)	0 (0–22.7)	0 (0–6.3)	0 (0–27.2)	2.4 (0.1–13.1)
NMSC, n (%)[a]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IR (95% CI)	0 (0–18.9)	0 (0–6.0)	0 (0–22.7)	0 (0–6.3)	0 (0–27.2)	0 (0–8.7)
MACE, n (%)[a]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IR (95% CI)	0 (0–18.9)	0 (0–6.0)	0 (0–22.7)	0 (0–6.3)	0 (0–27.2)	0 (0–8.7)
VTE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IR (95% CI)	0 (0–18.9)	0 (0–6.0)	0 (0–22.7)	0 (0–6.3)	0 (0–27.2)	0 (0–8.7)

MES, based on central read of endoscopy, was assessed at Week 8 of OCTAVE Induction 1 or 2 (baseline of OCTAVE Sustain). Only patients who had a MES of 0 or 1 at Week 8 of OCTAVE Induction 1 or 2 are included in this analysis. Data represent the safety analysis set (patients who received at least one dose of study medication in OCTAVE Sustain), which included 294 patients (tofacitinib 5 mg BID, N = 105; tofacitinib 10 mg BID, N = 88; placebo, N = 101)

AE Adverse event; *BID* Twice daily; *CI* Confidence interval; *GI* Gastrointestinal; *HZ* Herpes zoster; *IR* Incidence rate (number of patients with events per 100 patient-years of exposure); *MACE* Major adverse cardiovascular event; *MES* Mayo endoscopic subscore; *N* Number of patients in the specified category; *n* Number of patients with the specified safety event; *NMSC* Non-melanoma skin cancer; *VTE* Venous thromboembolism

[a] Adjudicated events

[b] Excludes tuberculosis and HZ with two adjacent dermatomes

[c] Excludes preferred terms of pilonidal cyst, perirectal abscess, rectal abscess, anal abscess, perineal abscess, and any preferred terms using the term fistula

10 mg BID may improve the probability of successful maintenance therapy with tofacitinib 5 mg BID.

Abbreviations

5-ASA	5-aminosalicylates
AE	Adverse event
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
FAS	Full analysis set
GI	Gastrointestinal
HR	Hazard ratio
HZ	Herpes zoster
IR	Incidence rate
MACE	Major adverse cardiovascular events
MES	Mayo endoscopic subscore
N1	Number of patients in each subgroup with non-missing data
NMSC	Non-melanoma skin cancer
OI	Opportunistic infection
OR	Odds ratio
SD	Standard deviation
TNFi	Tumor necrosis factor inhibitor
UC	Ulcerative colitis
VTE	Venous thromboembolism

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available in order to ensure the protection of patient privacy in compliance with the EU General Data Protection Regulation (GDPR) but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. Study protocols were approved by the Institutional Review Boards and/or independent ethics committees at each of the investigational centers participating in the studies, or a central Institutional Review Board (Australia: Eastern Health Research and Ethics Committee; Royal Adelaide Hospital Research Ethics Committee; Sydney Local Health District Human Research Ethics Committee—CRGH; Monash Health Human Research Ethics; ACT Health Human Research Ethics Committee; and Ethics Review Committee of the Sydney Local Health District (SLHD) (RPAH ZONE); Austria: Ethik Kommission der Medizinischen Universitaet Wien; Belgium: Commisse Medische Ethiek van Universitaire Ziekenhuizen K.U; Brazil: Comite de Etica em Pesquisa do Hospital de Clinicas de Porto Alegre—HCPA/UFRGS; CONEP—Comissao Nacional de Etica em Pesquisa; and Comite de Etica em Pesquisa do Hospital Universitario Clementino Fraga Filho/UFRJ; Canada: Comite d'ethique de la recherche de l'hopital Maisonneuve-Rosemont; Montreal General Hospital—McGill University Health Centre; Western University Health Sciences Research Ethics Board; University of Saskatchewan BioMedical Research Ethics Board (Bio-REB); Hamilton Integrated Research Ethics Board; University of Alberta-Health Research Ethics Board; and Conjoint Health Research Ethics Board; Colombia: Comite de Etica en Investigación en el Area de la Salud de la Universidad del Norte; Comite de Investigaciones y Etica en Investigaciones del Hospital Pablo Tobon Uribe; and Comite de Estudios Medicos S.A.S.—CRE-IMED S.A.S.; Croatia: Agency for Medicinal Products and Medical Devices of Croatia, Central Ethics Committee, RoC; Czech Republic: Eticka komise IKEM a TN; Eticka komise Nemocnice Strakonice, a.s.; Eticka komise klinickeho centra ISCARE; Eticka komise Krajska zdravotni, a.s.—Masarykova nemocnice v Usti nad Labem, o.z.; and Etická komise Fakultni nemocnice Hradec Kralove; Denmark: Den Videnskabsetiske Komité for Region Syddanmark; Estonia: Tallinn Medical Research Ethics Committee; France: Comite de Protection des Personnes Ile de France VIII; Germany: Ethik Kommission Kiel der Medizinischen Fakultaet der Christian-Albrechts-Universitaet zu Kiel; Hungary: Egeszsegugyi Tudomanyos Tanacs Klinikai Farmakologiai Etikai Bizottsaga; Israel: Helsinki Committee-The Edith Wolfson Medical Center; Helsinki Committee Rabin Medical Center; Helsinki Committee Rambam Health Care Campus; Helsinki Committee Tel Aviv Sourasky Medical Center; and Helsinki Committee Kaplan Medical Center; Italy: Comitato Etico Indipendente del Centro di Riferimento Oncologico di Aviano; Comitato Etico Istituto Clinico Humanitas IRCCS; Comitato Etico Palermo 2; and Comitato Etico Azienda Ospedaliera Universitaria "Mater Domini"; Japan: National Hospital Organization CRB; Osaka City University Hospital IRB; Osaka Medical College Hospital Institutional Review Board; Japan Community Health care Organization Tokyo Yamate Medical Center Institutional Review Board; Tokai University Hospital Institutional Review Board; Institutional Review Board of Keio University Hospital; Kitasato University Kitasato Institute Hospital Institutional Review Board; Chiba University Hospital IRB; National Hospital Organization Central Review Board; Aichi Medical University Hospital IRB; Kurume University Hospital Institutional Review Board; Keiaikai Institutional Review Board; Kyoto University Hospital Institutional Review Board; Jikei University Hospital Institutional Review Board; Showa University Hospital Institutional Review Board; Fukuoka University Chikushi Hospital Institutional Review Board; The Hospital of Hyogo College of Medicine IRB; Toho University Sakura Medical Center Institutional Review Board; Hiroshima University Hospital Institutional Review Board; Yokohama minoru medical Clinic IRB; NTT Medical Center Tokyo Institutional Review Board; Sapporo-Kosei General Hospital IRB; Tokyo Medical And Dental University Hospital, Faculty of Medicine Institutional Review Board; Shiga University of Medical Science Hospital Institutional Review Board; and Yokohama minoru medical Clinic IRB; Korea: Gachon University Gil Medical Center IRB; Hanyang University Guri Hospital Institutional Review Board; Kyung Hee University Hospital Institutional Review Board; Seoul National University Hospital IRB; Severance Hospital, Yeonsei University Health System; Samsung Medical Center; IRB of Pusan National University Hospital; Asan Medical Center Institutional Review Board; and CHA Bundang Medical Center, CHA University Institutional Review Board; Latvia: EC for Clinical Research at Development Society; Netherlands: Medisch Ethische Toetsingscommissie (METC); New Zealand: Southern Health and Disability Ethics Committee; Poland: Komisja Etyki i Nadzoru nad Badaniami na Ludziach i Zwierzetach Centralnego Szpitala Klinicznego MSWiA w Warszawie; Komisja Bioetyczna przy Okregowej Izbie Lekarskiej; and Diagnostyka Sp. z o.o.; Romania: Ministerul Sanatatii, Comisia Nationala de Etica pentru Studiul Clinic al Medicamentuli; and Comisia Nationala de Bioetica a Medicamentului; Russian Federation: Ethics Committee at State budget Institution of Healthcare; Ethics Council of Ministry of Health and Social Development of the Russian Federation; Independent Ethics Committee attached to Moscow regional scientific research clinical institute named after M.F. Vladimirsky; Ethics Committee attached to FSBI "State scientific centre of coloproctology" of Ministry of Health of Russian Federation; Ethics Committee of Yaroslavl State Medical Academy; Ethics committee attached to SBIH of Yaroslavl region Regional clinical hospital; Ethics committee attached to Municipal Budget Institution of Healthcare "Central City Hospital of Pyatigorsk"; Institution of Higher Professional Education "Saratov State Medical University named after V.I. Razumovsky"; Ethics Committee of State Budget Educational of Healthcare City Hospital No

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26; Ethics Committee of State Budget Educational institution of Higher Professional Education; Ethics Committee at 7A, Myagi str., Limited Liability Company Medical Company "Hepatolog"; and Biomedical EC of FSBI of PFM of the SD of RAMS; Serbia: Ethics Committee of Clinical Centre of Vojvodina; Ethics Com. Clinical Hospital Centre Zvezdara; Ethics Committee of Clinical Centre of Serbia; Ethics Committee Clinical Centre of Nis; Ethics Committee of General Hospital "Djordje Joanovic"; Ethics Committee of Military Medical Academy; Ethics Committee, General Hospital Subotica; and Ethics Committee of Clinical Centre of Kragujevac; Slovakia: MEC: Eticka Komisia, Urad Nitrianskeho samospravneho kraja; LEC: Eticka komisia, NsP Nove Mesto; MEC/LEC Eticka Komisia,Urad Nitrianskeho samospravneho kraja; Urad Bratislavskeho samospravneho kraja, Eticka komisia; Eticka komisia UN Bratislava Nemocnica Stare Mesto; Eticka komisia Trencianskeho samospravneho kraja; Eticka komisia Presovskeho samospravneho kraja; South Africa: Pharma-Ethics [Pty] Ltd; and University of the Witwatersrand Human Research Ethics committee; Spain: CEIC Hospital Clinic I Provincial de Barcelona; and CEIC Area 7. Hospital Clinico San Carlos; Taiwan: Research Ethics Committee of National Taiwan University Hospital; Ukraine: Ethics Commission of Vinnytsia; LEC of Municipal Healthcare Institution "Kharkiv City Clinical Hospital #2"; The Central Ethics Commission of the Ministry of Health of Ukraine; Commission of Ethic Questions of Kyiv Municipal Clinical Hospital #18; LEC of the State Institution "L.T. Malaya Therapy Institute of National Academy Department of Liver and Gastro-Intestinal Tract Diseases of Medical Sciences of Ukraine"; Ethics Commission at Kyiv City Clinical Hospital#8; E.C. of C. R. I. "Clinical Territorial Medical Community""University Clinic"; Local Ethics Commission of Regional Municipal I; Ethics Commission at State Institution Railway Hos; Ethics Commission of State Institution "Institute of Gastroenterology of the Academy of Medical Sciences of Ukraine"; LEC of the Municipal Institution City Hospital #7; LEC of S.I. "District Clinical Hospital""Lviv Railway"; Ethics Commission of Municipal Institution "Odesa Regional Clinical Hospital"; and Local Ethics Commission of Regional Municipal Institution Chernivtsi Regional Clinical Hospital; UK: NRES Committee London—Riverside; and USA: Baylor College of Medicine; Quorum Institutional Review Board; Quorum Institutional Review Board; The IRB of The Guthrie Clinic; IRBMED; Western Institutional Review Board; Mayo Clinic Institutional Review Board; Program for the Protection of Human Subjects Mount Sinai Medical Center; Cedars Sinai Office of Research Compliance; Human Research Protections Program (HRPP); Aurora IRB; University of California San Francisco Committee on Human Research; Human Research Protection Office, Washington University School in St. Louis; Cleveland Clinic Foundation Institutional Review Board; Yale University Human Research Protection Program; Chesapeake Institutional Review Board; Human Research Protection Program; Saint Joseph Mercy Health System IRB and Research Compliance; and Columbia University Medical Center IRB). All the patients provided written informed consent.

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