ORIGINAL ARTICLE

Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

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ABSTRACT

BACKGROUND

Tofacitinib, an oral, small-molecule Janus kinase inhibitor, was shown to have potential efficacy as induction therapy for ulcerative colitis in a phase 2 trial. We further evaluated the efficacy of tofacitinib as induction and maintenance therapy.

METHODS

We conducted three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in adults with ulcerative colitis. In the OCTAVE Induction 1 and 2 trials, 598 and 541 patients, respectively, who had moderately to severely active ulcerative colitis despite previous conventional therapy or therapy with a tumor necrosis factor antagonist were randomly assigned to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks. The primary end point was remission at 8 weeks. In the OCTAVE Sustain trial, 593 patients who had a clinical response to induction therapy were randomly assigned to receive maintenance therapy with tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks. The primary end point was remission at 52 weeks.

RESULTS

In the OCTAVE Induction 1 trial, remission at 8 weeks occurred in 18.5% of the patients in the tofacitinib group versus 8.2% in the placebo group ($P=0.007$); in the OCTAVE Induction 2 trial, remission occurred in 16.6% versus 3.6% ($P<0.001$). In the OCTAVE Sustain trial, remission at 52 weeks occurred in 34.3% of the patients in the 5-mg tofacitinib group and 40.6% in the 10-mg tofacitinib group versus 11.1% in the placebo group ($P<0.001$ for both comparisons with placebo). In the OCTAVE Induction 1 and 2 trials, the rates of overall infection and serious infection were higher with tofacitinib than with placebo. In the OCTAVE Sustain trial, the rate of serious infection was similar across the three treatment groups, and the rates of overall infection and herpes zoster infection were higher with tofacitinib than with placebo. Across all three trials, adjudicated nonmelanoma skin cancer occurred in five patients who received tofacitinib and in one who received placebo, and adjudicated cardiovascular events occurred in five who received tofacitinib and in none who received placebo; as compared with placebo, tofacitinib was associated with increased lipid levels.

CONCLUSIONS

In patients with moderately to severely active ulcerative colitis, tofacitinib was more effective as induction and maintenance therapy than placebo. (Funded by Pfizer; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain ClinicalTrials.gov numbers, NCT01465763, NCT01458951, and NCT01458574, respectively.)

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*A complete list of investigators in the OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain trials is provided in the Supplementary Appendix, available at NEJM.org.

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Ulcerative colitis is characterized by an increased frequency of bowel movements and bloody diarrhea, which has a negative effect on quality of life.[1] Current therapies for ulcerative colitis include mesalamine, glucocorticoids, thiopurines, and antagonists to tumor necrosis factor (TNF) and $\alpha 4\beta 7$ integrin.[1-5] Many patients do not have a response to these therapies or have a response that is not sustained. Additional treatment options with new mechanisms of action are needed to increase efficacy rates.

The Janus kinase (JAK) family comprises four intracellular tyrosine kinases — JAK1, JAK2, JAK3, and nonreceptor tyrosine-protein kinase 2 — that activate signal transducers and activators of transcription (STATs) through autophosphorylation.[6,7] JAK-STAT pathways regulate signaling for multiple immune-relevant mediators, including type I interferon, interferon-γ, and interleukins 2, 4, 6, 7, 9, 12, 15, 21, 23, and 27,[6,7] and they are implicated in the pathogenesis of inflammatory bowel diseases.[8,9] Tofacitinib is an oral, small-molecule JAK inhibitor that is being investigated for the treatment of ulcerative colitis. Tofacitinib inhibits all JAKs but preferentially inhibits JAK1 and JAK3,[10,11] and it was shown to have dose-dependent efficacy as induction therapy for ulcerative colitis in a phase 2 trial.[12] We report the results of three phase 3 trials, two investigating tofacitinib as induction therapy (OCTAVE Induction 1 and 2) and one investigating tofacitinib as maintenance therapy (OCTAVE Sustain) for ulcerative colitis.

Methods

Trial Design and Oversight

From April 2012 through May 2016, we conducted three multicenter, randomized, double-blind, placebo-controlled trials: OCTAVE Induction 1, which was conducted at 144 sites worldwide; OCTAVE Induction 2, at 169 sites; and OCTAVE Sustain, at 297 sites. The trial protocols (available with the full text of this article at NEJM.org) were approved by the institutional review board or independent ethics committee at each participating center. All the patients provided written informed consent.

The trials were funded by Pfizer. Personnel from Pfizer designed the trials in conjunction with the principal academic investigators. A contract research organization (ICON) collected the trial data, Pfizer analyzed the data, and all the authors jointly interpreted the data. The first and last authors wrote the first draft of the manuscript, and all the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. The authors vouch for the veracity and completeness of the data and analyses and for the fidelity of the trial to the protocol. Editorial support was funded by Pfizer.

Patients

In the OCTAVE Induction 1 and 2 trials, patients were 18 years of age or older and had had a confirmed diagnosis of ulcerative colitis for at least 4 months. Patients had moderately to severely active disease, which was defined as a Mayo score of 6 to 12, with a rectal bleeding subscore of 1 to 3 and an endoscopic subscore of 2 or 3.[13,14] Scores on the Mayo scale range from 0 to 12, and scores on each of the four subscores range from 0 to 3, with higher scores indicating more severe disease. Eligibility for the trial was based on a centrally assessed Mayo endoscopic subscore. Exclusion criteria were the presence of clinical findings suggestive of Crohn's disease, ulcerative colitis limited to the distal 15 cm of colon, clinical signs of fulminant colitis, toxic megacolon, or indeterminate, microscopic, ischemic, or infectious colitis. Patients were required to have had treatment failure with or to have had unacceptable side effects from treatment with at least one of the following agents: oral or intravenous glucocorticoids, azathioprine, mercaptopurine, infliximab, or adalimumab. Permitted concomitant medications for ulcerative colitis were oral aminosalicylates and oral glucocorticoids (at a maximum dose of 25 mg per day of prednisone or a prednisone equivalent), provided that the medications were administered at a stable dose throughout the induction trials; in the maintenance trial, tapering of glucocorticoids was mandatory. Prohibited concomitant therapies included TNF antagonists, azathioprine, methotrexate, and mercaptopurine. For further details about the selection criteria, see the Supplementary Appendix, available at NEJM.org.

Patients who completed the OCTAVE Induction 1 or 2 trial and had a clinical response during the induction trial were eligible to participate in the OCTAVE Sustain trial (see Fig. S1 in the Supplementary Appendix). Clinical response was defined as a decrease from induction-trial baseline in the total Mayo score of at least 3 points

and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. Definitions of end points that are based on the Mayo score are provided in Table S1 in the Supplementary Appendix.[13] Patients who met the criteria for treatment failure and received rescue therapy (including surgery) were withdrawn.

RANDOMIZATION AND TREATMENTS

In the OCTAVE Induction 1 and 2 trials, eligible patients were randomly assigned, in a 4:1 ratio, to receive induction therapy with oral tofacitinib at a dose of 10 mg twice daily or placebo for 8 weeks. The induction trials initially included groups that received tofacitinib at a dose of 15 mg twice daily, but Pfizer decided to discontinue further exploration of this dose. This decision was not based on any new safety data or a new interpretation of the existing safety data generated across multiple indications, including ulcerative colitis; rather, it was based on feedback received from regulatory authorities for rheumatoid arthritis. The protocol was amended, and randomization to the 15-mg tofacitinib group was ceased after 38 patients in the OCTAVE Induction 1 trial and 18 patients in the OCTAVE Induction 2 trial had undergone randomization across three treatment groups. Patients who entered the OCTAVE Sustain trial were randomly assigned again, in a 1:1:1 ratio, to receive maintenance therapy with tofacitinib at a dose of 5 mg twice daily, tofacitinib at a dose of 10 mg twice daily, or placebo for 52 weeks.

For the OCTAVE Induction 1 and 2 trials, dose selection was based on dose-response data with respect to clinical remission at 8 weeks in a phase 2, placebo-controlled trial that evaluated tofacitinib at doses of 0.5 mg, 3 mg, 10 mg, and 15 mg twice daily in patients with ulcerative colitis; the largest treatment effects were seen with the 10-mg and 15-mg doses.[12,15] For the OCTAVE Sustain trial, doses were selected to evaluate the efficacy of tofacitinib at the same dose evaluated in the induction trials (10 mg twice daily) and at a lower dose (5 mg twice daily).

Randomization was performed centrally with the use of a telerandomization system and was stratified in the OCTAVE Induction 1 and 2 trials according to previous treatment with TNF antagonists, glucocorticoid use at baseline, and geographic region and in the OCTAVE Sustain trial according to induction-trial group assignment and remission status at maintenance-trial entry.

EFFICACY AND SAFETY EVALUATIONS

The total Mayo score was determined at baseline and at 8 weeks in the induction trials and at 24 and 52 weeks in the maintenance trial. The partial Mayo score (i.e., the total Mayo score excluding the endoscopic subscore, with scores ranging from 0 to 9 and higher scores indicating more severe disease) was determined at 0, 2, 4, and 8 weeks in the induction trials and at 4, 8, 16, 24, 32, 40, and 52 weeks in the maintenance trial. Mayo scores were calculated on the basis of centrally assessed endoscopic subscores. The score on the Inflammatory Bowel Disease Questionnaire (IBDQ, with scores ranging from 32 to 224 and higher scores indicating better quality of life) was determined at 0, 4, and 8 weeks in the induction trials and at 8, 16, 24, 32, 40, and 52 weeks in the maintenance trial. Efficacy data at 8 weeks in the induction trials were used as baseline data for the maintenance trial. Adverse events (which were classified with the use of the *Medical Dictionary for Regulatory Activities*), laboratory test results, and concomitant medications were recorded throughout all the trials. Opportunistic infections, cancers, and cardiovascular events were assessed by external adjudication committees. The plasma tofacitinib concentrations before and after dose administration were measured with the use of a validated assay at 2 and 8 weeks in the induction trials and at 8, 24, and 52 weeks in the maintenance trial.

END POINTS

In the OCTAVE Induction 1 and 2 trials, the primary efficacy end point was remission (a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0) at 8 weeks, and the key secondary end point was mucosal healing (a Mayo endoscopic subscore of ≤1) at 8 weeks. In the OCTAVE Sustain trial, the primary end point was remission at 52 weeks; key secondary end points were mucosal healing at 52 weeks and remission that was sustained (i.e., occurring at both 24 and 52 weeks) and glucocorticoid-free (i.e., occurring without the administration of glucocorticoids for ≥4 weeks before the assessment) among patients who were in remission at maintenance-trial entry. A complete list of end points for the three trials is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Binary end points, including the primary efficacy end points in the three trials, were compared between the tofacitinib and placebo groups with the use of a stratified Cochran–Mantel–Haenszel chi-square test. Patients with missing data were considered as not having had a response. The family-wise type 1 error rate was controlled at 0.05 for the primary and key secondary end points with the use of a fixed-sequence testing procedure in the induction trials and a sequentially rejective, Bonferroni-based, iterative multiple-test procedure[16] in the maintenance trial. In the induction trials, the change from baseline in the total Mayo score was analyzed with the use of an analysis of covariance model with observed case data. For other continuous end points, change from baseline was analyzed with the use of a linear mixed-effects model. The efficacy analyses were based on data from all patients who underwent randomization. The safety analyses were based on data from all patients who underwent randomization and received at least one dose of the assigned treatment. Both the efficacy and the safety analyses in the induction trials did not include data from patients who were assigned to receive tofacitinib at a dose of 15 mg; those data were analyzed separately.

For the OCTAVE Induction 1 and 2 trials, the sample size was estimated on the basis of the primary end point and the mucosal healing secondary end point. We calculated that a sample size of approximately 545 patients in each trial (436 patients assigned to receive tofacitinib and 109 patients assigned to receive placebo) would provide the trials with 90% power to detect a difference of 17.5 percentage points between the tofacitinib groups and the placebo groups in the rates of the primary and key secondary end points, assuming rates in the placebo groups of 15% for the primary end point and 35% for the mucosal healing secondary end point. For the OCTAVE Sustain trial, the predicted sample size of 654 patients was based on an assumed clinical response rate of 65% in the tofacitinib groups and 40% in the placebo groups at 8 weeks in the induction trials. We calculated that a sample size of 654 patients (218 in each of the three treatment groups) would provide the trial with 90% power to detect a difference of 17.5 percentage points between the tofacitinib groups and the placebo group in the rate of the primary end point, assuming a rate in the placebo group of 30%.

The average plasma tofacitinib concentration during a dosing interval was estimated with the use of a population pharmacokinetic model that included data on plasma tofacitinib concentration relative to time that were pooled from all induction and maintenance studies involving patients with ulcerative colitis. The distribution of individualized average concentrations was compared between patients who were in remission and those who were not in remission with the use of box plots.

RESULTS

PATIENT CHARACTERISTICS

In the OCTAVE Induction 1 trial, 614 patients underwent randomization: 122 were assigned to receive placebo, 476 to receive tofacitinib at a dose of 10 mg twice daily, and 16 to receive tofacitinib at a dose of 15 mg twice daily. In the OCTAVE Induction 2 trial, 547 patients underwent randomization: 112 were assigned to receive placebo, 429 to receive tofacitinib at a dose of 10 mg twice daily, and 6 to receive tofacitinib at a dose of 15 mg twice daily.

In the OCTAVE Sustain trial, 593 patients underwent randomization: 198 were assigned to receive placebo, 198 to receive tofacitinib at a dose of 5 mg twice daily, and 197 to receive tofacitinib at a dose of 10 mg twice daily. The majority (88%) of patients in the OCTAVE Sustain trial had received tofacitinib during the induction trial, and 30% were in remission at maintenance-trial entry.

The baseline characteristics of the patients were similar across treatment groups in all the trials, except for sex in the OCTAVE Induction 2 trial and smoking status in the OCTAVE Sustain trial (Table 1, and Table S2 in the Supplementary Appendix). Details regarding the disposition of patients in each of the three trials are provided in Figures S2 and S3 in the Supplementary Appendix.

EFFICACY

Primary End Point

In the OCTAVE Induction 1 trial, remission at 8 weeks occurred in 18.5% of the patients (88 of 476) in the 10-mg tofacitinib group versus 8.2% (10 of 122) in the placebo group ($P=0.007$) — a difference of 10.3 percentage points (95% confi-

Table 1. Baseline Demographic and Disease Characteristics of the Patients in the OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Trials.*

Characteristic	OCTAVE Induction 1		OCTAVE Induction 2		OCTAVE Sustain		
	Placebo (N=122)	Tofacitinib, 10 mg (N=476)	Placebo (N=112)	Tofacitinib, 10 mg (N=429)	Placebo (N=198)	Tofacitinib, 5 mg (N=198)	Tofacitinib, 10 mg (N=197)
Male sex — no. (%)†	77 (63.1)	277 (58.2)	55 (49.1)	259 (60.4)	116 (58.6)	103 (52.0)	110 (55.8)
Age — yr‡	41.8±15.3	41.3±14.1	40.4±13.2	41.1±13.5	43.4±14.0	41.9±13.7	42.9±14.4
Induction-trial group assignment — no. (%)							
Placebo	—	—	—	—	24 (12.1)	22 (11.1)	24 (12.2)
Tofacitinib, 10 mg twice daily	—	—	—	—	167 (84.3)	170 (85.9)	167 (84.8)
Tofacitinib, 15 mg twice daily	—	—	—	—	7 (3.5)	6 (3.0)	6 (3.0)
Remission at maintenance-trial entry — no. (%)	—	—	—	—	59 (29.8)	65 (32.8)	55 (27.9)
Duration of disease — yr‡							
Median	6.0	6.5	6.2	6.0	7.2	6.5	6.8
Range	0.5–36.2	0.3–42.5	0.4–27.9	0.4–39.4	0.6–42.7	0.6–40.3	0.6–35.7
Extent of disease — no./total no. (%)§¶							
Proctosigmoiditis	19/122 (15.6)	65/475 (13.7)	16/111 (14.4)	67/428 (15.7)	21/198 (10.6)	28/196 (14.3)	33/196 (16.8)
Left-sided colitis	37/122 (30.3)	158/475 (33.3)	39/111 (35.1)	149/428 (34.8)	68/198 (34.3)	66/196 (33.7)	60/196 (30.6)
Extensive colitis or pancolitis	66/122 (54.1)	252/475 (53.1)	56/111 (50.5)	211/428 (49.3)	108/198 (54.5)	102/196 (52.0)	103/196 (52.6)
Total Mayo score‡‖	9.1±1.4	9.0±1.4	8.9±1.5	9.0±1.5	3.3±1.8	3.3±1.8	3.4±1.8
Partial Mayo score‡‖	6.5±1.2	6.3±1.2	6.4±1.2	6.4±1.3	1.8±1.4	1.8±1.3	1.8±1.3
C-reactive protein — mg/liter‡							
Median	4.7	4.4	5.0	4.6	1.0	0.7	0.9
Range	0.1–82.5	0.1–208.4	0.2–205.1	0.2–156.0	0.1–45.0	0.1–33.7	0.1–74.3
Oral glucocorticoid use at baseline — no. (%)‡	58 (47.5)	214 (45.0)	55 (49.1)	198 (46.2)	100 (50.5)	101 (51.0)	87 (44.2)
Previous treatment with TNF antagonist — no. (%)§	65 (53.3)	254 (53.4)	65 (58.0)	234 (54.5)	92 (46.5)	90 (45.5)	101 (51.3)
Previous treatment failure — no. (%)§**							
TNF antagonist	64 (52.5)	243 (51.1)	60 (53.6)	222 (51.7)	89 (44.9)	83 (41.9)	93 (47.2)
Glucocorticoid	98 (80.3)	350 (73.5)	83 (74.1)	303 (70.6)	151 (76.3)	145 (73.2)	149 (75.6)
Immunosuppressant††	83 (68.0)	360 (75.6)	75 (67.0)	301 (70.2)	129 (65.2)	143 (72.2)	141 (71.6)

* Plus–minus values are means ±SD. There were no significant differences between groups within each trial unless otherwise noted. TNF denotes tumor necrosis factor.
† In the OCTAVE Induction 2 trial, there was a significant difference between groups in the proportion of male patients (P=0.03).
‡ For the OCTAVE Sustain trial, the baseline values were obtained at the time of entry in the OCTAVE Sustain trial.
§ For the OCTAVE Sustain trial, the baseline values were obtained at the time of entry into one of the induction trials (OCTAVE Induction 1 or 2).
¶ Data on extent of disease are missing for three patients.
‖ The total Mayo score ranges from 0 to 12 and the partial Mayo score (i.e., the total Mayo score excluding the endoscopic subscore) ranges from 0 to 9, with higher scores indicating more severe disease.
** Previous treatment failure was determined by the investigator.
†† Immunosuppressants included agents such as azathioprine and mercaptopurine and did not include biologic agents (e.g., TNF antagonists) or glucocorticocoids.

dence interval [CI], 4.3 to 16.3). In the OCTAVE Induction 2 trial, remission at 8 weeks occurred in 16.6% of the patients (71 of 429) in the 10-mg tofacitinib group versus 3.6% (4 of 112) in the placebo group (P<0.001) — a difference of 13.0 percentage points (95% CI, 8.1 to 17.9). In both trials, the treatment effect was similar between those who had received previous treatment with a TNF antagonist and those who had not (Fig. S4 in the Supplementary Appendix). Results for the 15-mg tofacitinib groups are shown in Table S3 in the Supplementary Appendix.

In the OCTAVE Sustain trial, remission at 52 weeks occurred in 34.3% of the patients (68 of 198) in the 5-mg tofacitinib group and in 40.6% (80 of 197) in the 10-mg tofacitinib group, as compared with 11.1% (22 of 198) in the placebo group (P<0.001 for both comparisons with placebo) (Fig. 1, and Fig. S5 in the Supplementary Appendix). The difference between tofacitinib at a dose of 5 mg twice daily and placebo was 23.2 percentage points (95% CI, 15.3 to 31.2), and the difference between tofacitinib at a dose of 10 mg twice daily and placebo was 29.5 percentage points (95% CI, 21.4 to 37.6).

Secondary End Points

In the OCTAVE Induction 1 and 2 trials, the key secondary end point of mucosal healing at 8 weeks occurred in significantly more patients in the 10-mg tofacitinib groups than in the placebo groups (Fig. 1 and Table 2). The treatment effect was similar between those who had received previous treatment with a TNF antagonist and those who had not (Fig. S6 in the Supplementary Appendix).

In the OCTAVE Sustain trial, mucosal healing at 52 weeks occurred in significantly more patients in the 5-mg tofacitinib group (37.4% of patients [74 of 198]) and in the 10-mg tofacitinib group (45.7% [90 of 197]) than in the placebo group (13.1% [26 of 198]) (P<0.001 for both comparisons) (Fig. 1). Among patients who were in remission at maintenance-trial entry, sustained and glucocorticoid-free remission occurred in 35.4% (23 of 65) in the 5-mg tofacitinib group and in 47.3% (26 of 55) in the 10-mg tofacitinib group versus 5.1% (3 of 59) in the placebo group (P<0.001 for both comparisons) (Table 3). Details about additional secondary end points in the OCTAVE Sustain trial are provided in Table S4 in the Supplementary Appendix.

In the OCTAVE Induction 1 and 2 trials, improvement from baseline in the partial Mayo score was significantly greater in the 10-mg tofacitinib groups than in the placebo groups at all scheduled visits and as early as week 2 (the first assessment of the partial Mayo score after the baseline assessment) (P<0.001 for all comparisons) (Fig. S7 in the Supplementary Appendix). In the OCTAVE Sustain trial, improvement from maintenance-trial baseline in the partial Mayo score was significantly greater in both tofacitinib groups than in the placebo group at all study visits (P<0.001 for all comparisons). Data on the mean change from baseline in the C-reactive protein level in all three trials are shown in Figure S8 in the Supplementary Appendix. The majority of the decrease from baseline in C-reactive protein level had occurred by week 4 (the first assessment of C-reactive protein level after the baseline assessment) in both induction trials.

Patient-Reported End Points

The mean IBDQ total scores at baseline were between 118 and 125 in the induction trials and between 181 and 182 in the maintenance trial. The proportion of patients with an IBDQ score indicative of remission (i.e., a score of ≥170) and the proportion of patients with an IBDQ score indicative of a treatment response (i.e., a score ≥16 points higher than the baseline score in the induction trial) were significantly larger with tofacitinib than with placebo at weeks 4 and 8 in both induction trials (P≤0.004 for all comparisons) (Table 2) and at all visits in the maintenance trial (P<0.001 for all comparisons) (Table 3, and Table S4 in the Supplementary Appendix).

Pharmacokinetics

The estimated mean oral clearance of tofacitinib was 26.3 liters per hour, and the estimated mean oral volume of distribution of tofacitinib was 115.8 liters. The half-life of tofacitinib was 3 hours. There was no clinically meaningful effect of age, sex, body weight, or disease severity at baseline (i.e., baseline albumin level and Mayo score) on tofacitinib oral clearance and thus on the average plasma tofacitinib concentration (which is inversely proportional to clearance). The oral clearance of tofacitinib, and thus the average concentration at a given dose in individual patients, did not change significantly during the course of induction and maintenance treatment. The average concentration after a dose was administered was similar between patients who were in remission

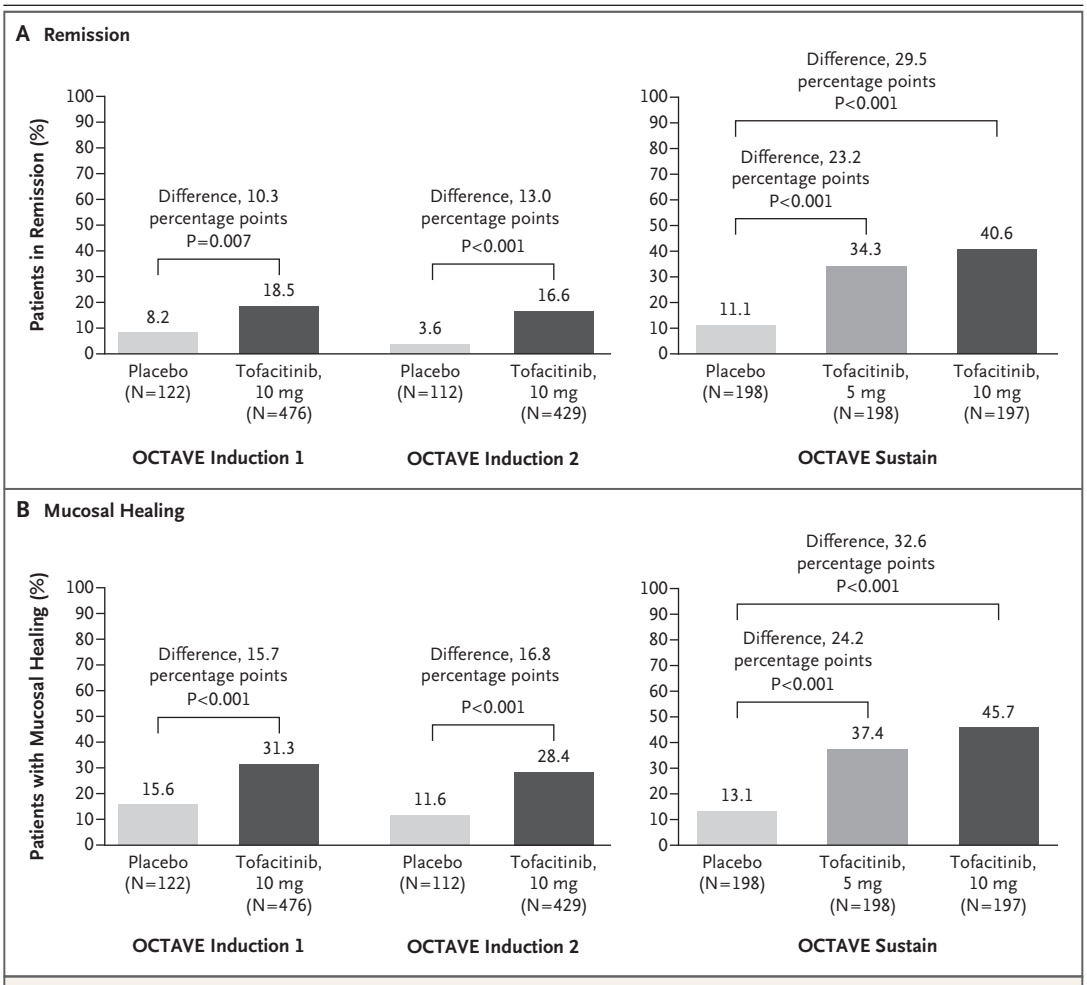

Figure 1. Primary and Key Secondary End Points.

Panel A shows the rate of remission (primary end point) and Panel B shows the rate of mucosal healing (key secondary end point) at 8 weeks among patients who received tofacitinib at a dose of 10 mg twice daily and those who received placebo (in the OCTAVE Induction 1 and 2 trials) and at 52 weeks among patients who received tofacitinib at a dose of 5 mg twice daily, those who received tofacitinib at a dose of 10 mg twice daily, and those who received placebo (in the OCTAVE Sustain trial).

and those who were not in remission at 8 weeks (in the induction trials) and at 52 weeks (in the maintenance trial) (Fig. S9 in the Supplementary Appendix). No subgroup of patients had loss of efficacy due to a decrease in the average concentration during treatment. In the maintenance trial, the average concentration increased proportionately with the dose.

SAFETY

In the OCTAVE Induction 1 trial, adverse events occurred in 56.5% of the patients (269 of 476) in the 10-mg tofacitinib group and in 59.8% (73 of 122) in the placebo group. The corresponding percentages in the OCTAVE Induction 2 trial were 54.1% (232 of 429) and 52.7% (59 of 112). Safety data for the 15-mg tofacitinib groups are shown in Table S5 in the Supplementary Appendix.

In the OCTAVE Sustain trial, adverse events occurred in 72.2% of the patients (143 of 198) in the 5-mg tofacitinib group, 79.6% (156 of 196) in the 10-mg tofacitinib group, and 75.3% (149 of 198) in the placebo group. The most frequently reported adverse events in any treatment group in the maintenance trial (excluding worsening ulcerative colitis) were nasopharyngitis, arthralgia, and headache (Table 4).

In the OCTAVE Induction 1 trial, serious adverse events occurred in 3.4% of the patients in the 10-mg tofacitinib group and in 4.1% in the

Table 2. Efficacy Outcomes in the OCTAVE Induction 1 and OCTAVE Induction 2 Trials.*

End Point	OCTAVE Induction 1				OCTAVE Induction 2			
	Placebo (N=122)	Tofacitinib, 10 mg (N=476)	Difference (95% CI)	P Value	Placebo (N=112)	Tofacitinib, 10 mg (N=429)	Difference (95% CI)	P Value
			percentage points				*percentage points*	
Based on Mayo score†								
Primary end point: remission at wk 8 — no. (%)	10 (8.2)	88 (18.5)	10.3 (4.3 to 16.3)	0.007	4 (3.6)	71 (16.6)	13.0 (8.1 to 17.9)	<0.001
Mucosal healing at wk 8 — no. (%)	19 (15.6)	149 (31.3)	15.7 (8.1 to 23.4)	<0.001	13 (11.6)	122 (28.4)	16.8 (9.5 to 24.1)	<0.001
Clinical response at wk 8 — no. (%)	40 (32.8)	285 (59.9)	27.1 (17.7 to 36.5)	<0.001	32 (28.6)	236 (55.0)	26.4 (16.8 to 36.0)	<0.001
Clinical remission at wk 8 — no. (%)	10 (8.2)	88 (18.5)	10.3 (4.3 to 16.3)	0.007	4 (3.6)	72 (16.8)	13.2 (8.3 to 18.1)	<0.001
Endoscopic remission at wk 8 — no. (%)	2 (1.6)	32 (6.7)	5.1 (1.9 to 8.3)	0.04	2 (1.8)	30 (7.0)	5.2 (1.8 to 8.6)	0.04
Symptomatic remission at wk 8 — no. (%)	7 (5.7)	56 (11.8)	6.0 (1.0 to 11.1)	0.06	3 (2.7)	46 (10.7)	8.0 (3.9 to 12.2)	0.009
Deep remission at wk 8 — no. (%)	0	31 (6.5)	6.5 (4.3 to 8.7)	0.004	2 (1.8)	22 (5.1)	3.3 (0.1 to 6.6)	0.14
Change from baseline in total Mayo score at wk 8	−1.8±0.3	−3.8±0.1	−1.9 (−2.5 to −1.4)	<0.001	−2.1±0.3	−3.7±0.1	−1.6 (−2.2 to −1.0)	<0.001
Based on IBDQ score‡								
Remission at wk 4 — no. (%)	42 (34.4)	233 (48.9)	14.5 (5.0 to 24.1)	0.004	28 (25.0)	178 (41.5)	16.5 (7.2 to 25.8)	0.002
Remission at wk 8 — no. (%)	46 (37.7)	250 (52.5)	14.8 (5.1 to 24.5)	0.004	29 (25.9)	212 (49.4)	23.5 (14.1 to 32.9)	<0.001
Treatment response at wk 4 — no. (%)	63 (51.6)	342 (71.8)	20.2 (10.5 to 30.0)	<0.001	57 (50.9)	309 (72.0)	21.1 (10.9 to 31.3)	<0.001
Treatment response at wk 8 — no. (%)	67 (54.9)	333 (70.0)	15.0 (5.3 to 24.8)	0.001	56 (50.0)	315 (73.4)	23.4 (13.3 to 33.6)	<0.001

* Plus–minus values are least-squares means ±SE.

† Definitions of all efficacy end points that are based on the Mayo score are provided in Table S1 in the Supplementary Appendix. The total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.

‡ The Inflammatory Bowel Disease Questionnaire (IBDQ) score ranges from 32 to 224, with higher scores indicating better quality of life. An IBDQ score of 170 or higher is indicative of remission, and an IBDQ score at least 16 points higher than the baseline score in the induction trial is indicative of a treatment response.

Table 3. Efficacy Outcomes in the OCTAVE Sustain Trial.

End Point	OCTAVE Sustain						
	Placebo (N=198)	Tofacitinib, 5 mg (N=198)	Difference vs. Placebo (95% CI)	P Value	Tofacitinib, 10 mg (N=197)	Difference vs. Placebo (95% CI)	P Value
			percentage points			*percentage points*	
Based on Mayo score*							
Primary end point: remission at wk 52 — no. (%)	22 (11.1)	68 (34.3)	23.2 (15.3–31.2)	<0.001	80 (40.6)	29.5 (21.4–37.6)	<0.001
Sustained remission — no. (%)	10 (5.1)	44 (22.2)	17.2 (10.6–23.7)	<0.001	50 (25.4)	20.3 (13.5–27.1)	<0.001
Remission at wk 52 among patients in remission at baseline — no./total no. (%)	6/59 (10.2)	30/65 (46.2)	36.0 (21.6–50.3)	<0.001	31/55 (56.4)	46.2 (31.0–61.4)	<0.001
Sustained remission among patients in remission at baseline — no./total no. (%)	3/59 (5.1)	24/65 (36.9)	31.8 (18.8–44.8)	<0.001	26/55 (47.3)	42.2 (27.9–56.5)	<0.001
Sustained and glucocorticoid-free remission among patients in remission at baseline — no./total no. (%)	3/59 (5.1)	23/65 (35.4)	30.3 (17.4–43.2)	<0.001	26/55 (47.3)	42.2 (27.9–56.5)	<0.001
Mucosal healing at wk 52 — no. (%)	26 (13.1)	74 (37.4)	24.2 (16.0–32.5)	<0.001	90 (45.7)	32.6 (24.2–41.0)	<0.001
Sustained mucosal healing — no. (%)	13 (6.6)	55 (27.8)	21.2 (14.1–28.3)	<0.001	65 (33.0)	26.4 (19.0–33.8)	<0.001
Mucosal healing at wk 52 among patients with mucosal healing at baseline — no./total no. (%)	12/101 (11.9)	44/105 (41.9)	30.0 (18.7–41.4)	<0.001	49/89 (55.1)	43.2 (31.1–55.3)	<0.001
Sustained mucosal healing among patients with mucosal healing at baseline — no./total no. (%)	9/101 (8.9)	35/105 (33.3)	24.4 (13.8–35.0)	<0.001	44/89 (49.4)	40.5 (28.7–52.3)	<0.001
Clinical response at wk 52 — no. (%)	40 (20.2)	102 (51.5)	27.8 (18.9–36.7)	<0.001	122 (61.9)	41.7 (32.9–50.5)	<0.001
Sustained clinical response — no. (%)	38 (19.2)	97 (49.0)	29.8 (20.9–38.7)	<0.001	117 (59.4)	40.2 (31.4–49.0)	<0.001
Based on IBDQ score†							
Remission at wk 52 — no. (%)	40 (20.2)	95 (48.0)	27.8 (18.9–36.7)	<0.001	113 (57.4)	37.2 (28.3–46.0)	<0.001
Treatment response at wk 52 — no. (%)	43 (21.7)	102 (51.5)	29.8 (20.8–38.8)	<0.001	117 (59.4)	37.7 (28.7–46.6)	<0.001

* Definitions for all efficacy end points that are based on the Mayo score are provided in Table S1 in the Supplementary Appendix. End points were considered to be sustained if they occurred at both 24 and 52 weeks and were considered to be glucocorticoid-free if they occurred without the administration of glucocorticoids for at least 4 weeks before the assessment. Baseline information was obtained at entry in the OCTAVE Sustain trial.

† The Inflammatory Bowel Disease Questionnaire (IBDQ) score ranges from 32 to 224, with higher scores indicating better quality of life. An IBDQ score of 170 or higher is indicative of remission, and an IBDQ score at least 16 points higher than the baseline score in the induction trial is indicative of a treatment response.

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placebo group. The corresponding percentages in the OCTAVE Induction 2 trial were 4.2% and 8.0%. In the OCTAVE Sustain trial, serious adverse events occurred in 5.1% of the patients in the 5-mg tofacitinib group, 5.6% in the 10-mg tofacitinib group, and 6.6% in the placebo group (Table 4).

In the OCTAVE Induction 1 and 2 trials, the proportion of patients who discontinued treatment because of adverse events was similar in the placebo groups and the tofacitinib groups. In the OCTAVE Sustain trial, the proportion was larger in the placebo group than in the tofacitinib groups.

In the OCTAVE Induction 1 and 2 trials, the percentages of patients with infections of any severity were higher in the 10-mg tofacitinib groups (23.3% and 18.2%, respectively) than in the placebo groups (15.6% and 15.2%). In the OCTAVE Sustain trial, infections occurred in 35.9% of the patients in the 5-mg tofacitinib group, 39.8% in the 10-mg tofacitinib group, and 24.2% in the placebo group (Table 4). In all three trials, the majority of infections were mild or moderate in severity. In the OCTAVE Induction 1 and 2 trials, serious infections occurred in 6 patients (1.3%) and 1 patient (0.2%), respectively, in the 10-mg tofacitinib groups and in no patients in the placebo groups. In the OCTAVE Sustain trial, serious infections occurred in 2 patients (1.0%) in the 5-mg tofacitinib group, 1 (0.5%) in the 10-mg tofacitinib group, and 2 (1.0%) in the placebo group. In the OCTAVE Induction 1 and 2 trials, herpes zoster infection occurred in 3 patients (0.6%) and 2 patients (0.5%), respectively, in the 10-mg tofacitinib groups and in 1 (0.8%) patient and no patients in the placebo groups. In the OCTAVE Sustain trial, herpes zoster infection occurred in 3 patients (1.5%) in the 5-mg tofacitinib group, 10 (5.1%) in the 10-mg tofacitinib group, and 1 (0.5%) in the placebo group. No cases of herpes zoster infection were serious adverse events or resulted in discontinuation; most affected one dermatome or two adjacent dermatomes (Table S7 in the Supplementary Appendix). One patient in the 10-mg tofacitinib group in the OCTAVE Induction 2 trial had cytomegalovirus colitis (see Section 6 in the Supplementary Appendix). No cases of tuberculosis were reported in the three trials.

In the OCTAVE Induction 1 trial, 1 patient in the 10-mg tofacitinib group had a serious adverse event of intestinal perforation. The patient had had cytomegalovirus colitis approximately 3 months before the start of the trial and had been receiving concomitant therapy with oral prednisone (20 mg daily) at baseline. The patient underwent colectomy and had a perforation in the descending colon, which had been affected by colitis. In the OCTAVE Induction 2 trial, 1 patient in the placebo group had a serious adverse event of intestinal perforation. No patients in the OCTAVE Sustain trial had adverse events of intestinal perforation. For further details, see the Supplementary Appendix.

In the induction trials, nonmelanoma skin cancers occurred in 2 patients: 1 patient in the 10-mg tofacitinib group in the OCTAVE Induction 1 trial who had a history of nonmelanoma skin cancer received a diagnosis of squamous-cell carcinoma of the skin, and 1 patient in the 10-mg tofacitinib group in the OCTAVE Induction 2 trial received a diagnosis of basal-cell carcinoma of the skin. In the OCTAVE Sustain trial, nonmelanoma skin cancers occurred in 4 patients: 3 patients in the 10-mg tofacitinib group who had a history of nonmelanoma skin cancer received a diagnosis of squamous-cell carcinoma (2) or basal-cell carcinoma (1), and 1 patient in the placebo group received a diagnosis of basal-cell carcinoma. All the patients with nonmelanoma skin cancer had previous exposure to thiopurines. No patients in the induction trials had cancer other than nonmelanoma skin cancer. One patient in the OCTAVE Sustain trial had invasive ductal breast carcinoma; this patient received placebo during both the induction trial and the maintenance trial. A list of neoplasms that occurred during the trials is provided in Table S8 in the Supplementary Appendix.

Across all three trials, 5 patients who received tofacitinib had adjudicated cardiovascular events. A list of cardiac disorders that occurred during the trials is provided in Table S9 in the Supplementary Appendix. One patient in the 10-mg tofacitinib group in the OCTAVE Induction 1 trial died from aortic dissection. For further details about adverse events, see the Supplementary Appendix.

In the induction and maintenance trials, the proportion of patients with abnormal lipid and creatine kinase levels was generally larger in the tofacitinib groups than in the placebo groups (Table 4). Across the three trials, lipid levels

Table 4. Safety Outcomes at 8 Weeks in the OCTAVE Induction 1 and 2 Trials and at 52 Weeks in the OCTAVE Sustain Trial.*

End Point	OCTAVE Induction 1		OCTAVE Induction 2		OCTAVE Sustain		
	Placebo (N=122)	Tofacitinib, 10 mg (N=476)	Placebo (N=112)	Tofacitinib, 10 mg (N=429)	Placebo (N=198)	Tofacitinib, 5 mg (N=198)	Tofacitinib, 10 mg (N=196)
Adverse events — no. (%)	73 (59.8)	269 (56.5)	59 (52.7)	232 (54.1)	149 (75.3)	143 (72.2)	156 (79.6)
Serious adverse events — no. (%)	5 (4.1)	16 (3.4)	9 (8.0)	18 (4.2)	13 (6.6)	10 (5.1)	11 (5.6)
Most frequent adverse events — no. (%)†							
Worsening ulcerative colitis	5 (4.1)	11 (2.3)	6 (5.4)	13 (3.0)	71 (35.9)	36 (18.2)	29 (14.8)
Nasopharyngitis	9 (7.4)	34 (7.1)	4 (3.6)	21 (4.9)	11 (5.6)	19 (9.6)	27 (13.8)
Arthralgia	6 (4.9)	14 (2.9)	6 (5.4)	11 (2.6)	19 (9.6)	17 (8.6)	17 (8.7)
Headache	8 (6.6)	37 (7.8)	9 (8.0)	33 (7.7)	12 (6.1)	17 (8.6)	6 (3.1)
Infections — no. (%)							
Any infection	19 (15.6)	111 (23.3)	17 (15.2)	78 (18.2)	48 (24.2)	71 (35.9)	78 (39.8)
Serious infection‡	0	6 (1.3)	0	1 (0.2)	2 (1.0)	2 (1.0)	1 (0.5)
Herpes zoster	1 (0.8)	3 (0.6)	0	2 (0.5)	1 (0.5)	3 (1.5)	10 (5.1)
Adverse events of special interest — no.							
Intestinal perforation§	0	1	1	0	0	0	0
Cancer other than nonmelanoma skin cancer¶	0	0	0	0	1‖	0	0
Nonmelanoma skin cancer¶	0	1	0	1	1	0	3
Cardiovascular events¶	0	2	0	2	0	1	1
Adverse events leading to discontinuation — no. (%)**	2 (1.6)	18 (3.8)	8 (7.1)	17 (4.0)	37 (18.7)	18 (9.1)	19 (9.7)
Abnormal laboratory test results — no./total no. (%)††							
Total cholesterol >1.3× ULN	11/122 (9.0)	80/471 (17.0)	6/111 (5.4)	73/424 (17.2)	16/198 (8.1)	54/198 (27.3)	44/195 (22.6)
Low-density lipoprotein >1.2× ULN	11/122 (9.0)	91/471 (19.3)	12/111 (10.8)	92/424 (21.7)	37/198 (18.7)	62/198 (31.3)	55/195 (28.2)
High-density lipoprotein <0.8× LLN	2/122 (1.6)	6/471 (1.3)	1/111 (0.9)	7/424 (1.7)	12/198 (6.1)	9/198 (4.5)	3/195 (1.5)
Triglycerides >1.3× ULN	1/122 (0.8)	15/471 (3.2)	2/111 (1.8)	12/424 (2.8)	7/198 (3.5)	9/198 (4.5)	15/195 (7.7)
Creatine kinase >2× ULN	2/122 (1.6)	45/474 (9.5)	10/112 (8.9)	40/425 (9.4)	14/198 (7.1)	37/198 (18.7)	54/195 (27.7)
Addition or increase in dose of lipid-lowering agent — no. (%)	0	4 (0.8)	1 (0.9)	2 (0.5)	3 (1.5)	2 (1.0)	8 (4.1)

* LLN denotes lower limit of the normal range, and ULN upper limit of the normal range.
† The rates of the four most frequent adverse events occurring in the OCTAVE Sustain trial are listed for all three trials.
‡ A list of serious infections that occurred during the trials is provided in Table S6 in the Supplementary Appendix.
§ These events were determined on the basis of the *Medical Dictionary for Regulatory Activities* preferred term.
¶ These events were determined on the basis of external adjudication.
‖ The cancer was invasive ductal breast carcinoma.
** These data include patients who discontinued treatment because of worsening ulcerative colitis.
†† Laboratory data were missing for some patients.

(total cholesterol, low-density lipoprotein, and high-density lipoprotein) increased with tofacitinib, and the increase plateaued after approximately 4 weeks (Table S10 in the Supplementary Appendix). There were no reported cases of myopathy or rhabdomyolysis associated with the elevated creatine kinase levels among patients who received tofacitinib. Across the three trials, 2 patients who received tofacitinib (both in the induction trials) had absolute lymphocyte counts of less than 500 per cubic millimeter that were confirmed by two sequential measurements; both patients had low absolute lymphocyte counts at baseline (640 and 650 per cubic millimeter).

DISCUSSION

In two identical phase 3 trials of induction therapy with tofacitinib in patients with moderately to severely active ulcerative colitis, the rates of remission at 8 weeks were significantly higher among those who received oral tofacitinib at a dose of 10 mg twice daily than among those who received placebo. The rates of mucosal healing and clinical response at 8 weeks were significantly higher and improvements in health-related quality of life were significantly greater with tofacitinib than with placebo. The onset of action was rapid, with significant improvement in the partial Mayo score observed at 2 weeks (the first assessment of the partial Mayo score after the baseline assessment). In a third phase 3 trial, which evaluated maintenance therapy with tofacitinib, efficacy with respect to these end points was maintained at 52 weeks with tofacitinib at a dose of either 5 mg or 10 mg twice daily. Treatment effect was significantly greater with tofacitinib at either dose than with placebo for all primary and secondary end points in the maintenance trial.

The OCTAVE trials incorporated a more stringent definition of remission (with the additional requirement of a rectal bleeding subscore of 0) than the definition used in previous trials of treatments for ulcerative colitis, such as the GEMINI 1 trial.[3] Furthermore, efficacy analyses in the OCTAVE trials were based on a centrally assessed Mayo endoscopic subscore. Analyses in prespecified subgroups, including subgroups defined according to previous treatment with TNF antagonists and treatment failure with TNF antagonists, showed a generally consistent treatment effect across most patient populations.

Tofacitinib is a nonbiologic small-molecule agent that is rapidly absorbed after oral administration of the immediate-release tablet. Pharmacokinetic results in the OCTAVE trials did not indicate a decrease in plasma tofacitinib concentrations during the course of treatment at any given dose in individual patients; these results are consistent with the previously established physicochemical characteristics and clearance mechanisms of tofacitinib.[17-19] In contrast, biologic therapies that are currently used for inflammatory bowel disease are susceptible to loss of exposure due to a high level of disease activity or immunogenicity and may warrant therapeutic drug monitoring.[20]

Among patients with rheumatoid arthritis or psoriasis,[21-25] tofacitinib has been associated with an increased risk of infections, including herpes zoster. In the OCTAVE trials, infections occurred at higher rates with tofacitinib than with placebo. The rate of serious infection was higher with tofacitinib in the induction trials but similar across treatment groups in the maintenance trial. A numerically higher rate of herpes zoster infection was observed in the 10-mg tofacitinib group than in the placebo group or the 5-mg tofacitinib group. Most cases of herpes zoster affected one dermatome or two adjacent dermatomes, and none led to discontinuation; these findings are consistent with findings seen with the use of tofacitinib for indications other than ulcerative colitis.[21-25]

Three patients who received tofacitinib in the induction trials and 1 patient in each tofacitinib group in the maintenance trial had adjudicated cardiovascular events. The size and duration of these trials limits the interpretation of these results. Among patients with rheumatoid arthritis or psoriasis,[21-25] tofacitinib has been associated with increases in certain lipid levels without an increased risk of cardiovascular events, a finding that is based on clinical-trial data from more than 6000 patients and more than 20,000 patient-years of tofacitinib exposure accumulated over a period of more than 8 years.

Gastrointestinal perforations have been observed with tofacitinib among patients with rheumatoid arthritis,[21-25] although the role of JAK inhibition in these events is unknown. Across

the OCTAVE trials, one intestinal perforation occurred with tofacitinib. More cases of nonmelanoma skin cancer occurred with tofacitinib than with placebo across the OCTAVE trials, a finding consistent with the potential for nonmelanoma skin cancer observed with the use of tofacitinib for other indications.[21-25]

The short duration of follow-up in the induction trials limited the ability to detect adverse events with low occurrence rates (particularly with placebo because of the randomization ratio of 4:1) and to evaluate the effect of induction therapy beyond 8 weeks. In the maintenance trial, efficacy and safety were evaluated over a period of 52 weeks among patients who had a clinical response during the induction trials, but data from the ongoing open-label extension trial (OCTAVE Open; ClinicalTrials.gov number, NCT01470612) of tofacitinib for the treatment of ulcerative colitis may further elucidate the long-term safety profile of tofacitinib. The risks of tofacitinib beyond 1 year among patients with ulcerative colitis are unknown.

In conclusion, among patients with moderately to severely active ulcerative colitis, therapy with tofacitinib at a dose of 10 mg twice daily was more effective than placebo for induction of remission and mucosal healing. Maintenance therapy with tofacitinib at a dose of either 5 mg or 10 mg twice daily was more effective than placebo in sustaining remission and mucosal healing.

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