Maintenance of Remission With Tofacitinib Therapy in Patients With Ulcerative Colitis

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BACKGROUND & AIMS: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). The efficacy and safety of tofacitinib in patients with moderate to severe UC, up to 1 year, have been reported. We investigated maintenance of efficacy in patients in remission after 52 weeks of maintenance treatment in the pivotal phase 3 study (OCTAVE Sustain); these patients received open-label, long-term treatment with tofacitinib 5 mg twice daily.

METHODS: Patients with moderate to severe UC who completed a 52-week, phase 3 maintenance study (OCTAVE Sustain) were eligible to enroll into the ongoing, phase 3, multicenter, open-label, long-term extension (OCTAVE Open). We analyzed data from 142 patients who were in remission following tofacitinib treatment in OCTAVE Sustain who received tofacitinib 5 mg twice daily during OCTAVE Open. We assessed efficacy (including remission [based on total Mayo score], endoscopic improvement, clinical response, and partial Mayo score up to month 36 of OCTAVE Open) and safety data.

RESULTS: After 12 months of tofacitinib 5 mg twice daily in OCTAVE Open, 68.3% of patients were in remission, 73.9% had endoscopic improvement, and 77.5% had a clinical response. At month 36, 50.4% of the patients were in remission, 55.3% had endoscopic improvement, and 56.0% had a clinical response. The safety profile of tofacitinib 5 mg twice daily revealed no new safety risks associated with long-term exposure up to 36 months.
CONCLUSIONS:

Efficacy endpoints were maintained for up to 36 months, regardless of prior tofacitinib dose, including patients who reduced from tofacitinib 10 mg to 5 mg twice daily upon OCTAVE Open entry. No new safety risks were identified. ClinicalTrials.gov: OCTAVE Sustain (NCT01458574); OCTAVE Open (NCT01470612).

Keywords: (3–4); JAK inhibitor; inflammatory bowel disease; response to therapy; active disease.

Patients with ulcerative colitis (UC) often require lifelong medical therapy to control symptoms and to avoid disease deterioration, hospitalization, and colectomy. Remission, defined in both symptomatic and endoscopic terms, represents a preferred goal of UC medical management strategies, with the ultimate goal being to achieve a sustained and durable period of steroid-free remission.

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of UC. The efficacy and safety of tofacitinib have been demonstrated in two 8-week, phase 3 induction studies (OCTAVE Induction 1 study [NCT01465763] and OCTAVE Induction 2 study [NCT01458951]) and a 52-week, phase 3 maintenance study (the OCTAVE Sustain study [NCT01458574]) in patients with moderate to severe UC.

Patients who completed the OCTAVE Sustain study, or had early treatment withdrawal due to treatment failure, were eligible to enroll into the open-label, long-term extension (OLE) study (OCTAVE Open study [NCT01470612]). Study treatment was assigned depending on the patients’ remission status at baseline of the OCTAVE Open study, with patients in remission assigned to receive tofacitinib 5 mg twice daily (BID), and patients who did not meet the remission definition assigned to receive tofacitinib 10 mg BID. The efficacy and safety of tofacitinib treatment in 2 patient subpopulations from the OCTAVE Open study that enrolled patients from the OCTAVE Induction 1 or 2 studies or the OCTAVE Sustain study have previously been reported. These analyses, reported by Sands et al., included 2 subgroups of patients: (1) tofacitinib induction responders in remission following 52 weeks of tofacitinib 10 mg BID maintenance treatment and subsequently reduced to tofacitinib 5 mg BID (the dose de-escalation group) and (2) tofacitinib induction responders who experienced treatment failure while receiving tofacitinib 5 mg BID maintenance treatment and subsequently increased to tofacitinib 10 mg BID (the dose escalation group). The primary aim of the current analysis was to investigate the maintenance of efficacy by examining a cohort of patients in remission after 52 weeks of tofacitinib treatment in the OCTAVE Sustain study, who subsequently received open-label, long-term treatment with tofacitinib 5 mg BID in the OCTAVE Open study. Maintenance of efficacy was assessed through the measurement of remission, endoscopic improvement, clinical response, and partial Mayo score (PMS). Patients’ steroid status was assessed throughout the OCTAVE Open study. The secondary aim was to report safety data for all patients who received tofacitinib 5 mg BID in the OCTAVE Open study (including those who entered the OCTAVE Sustain study in remission following treatment with placebo in the OCTAVE Sustain study).

Materials and Methods

Study Design

The OCTAVE Open study is an ongoing, phase 3, multicenter, OLE study that enrolled patients who completed or demonstrated treatment failure in the OCTAVE Sustain study, as well as patients who completed the OCTAVE Induction 1 and 2 studies without clinical response. Here, we report efficacy and safety data (up to May 2019) for patients who had completed the OCTAVE Sustain study and met the criteria for remission (defined as a total Mayo score ≤ 2, no individual subscore > 1, and a rectal bleeding subscore of 0) at week 52 and received open-label treatment with tofacitinib 5 mg BID during the OCTAVE Open study, independent of which treatment arm of the OCTAVE Sustain study they entered from (Figure 1). Remission status at week 52 of the OCTAVE Sustain study was based on centrally read Mayo endoscopic subscore. For further study design details, see the Supplementary Methods.

Ethical Considerations

All studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines, and were approved by the institutional review boards or independent ethics committees at each of the investigational centers participating in the studies, or a central institutional review board. All patients provided written informed consent.

Patient Disposition

Inclusion and exclusion criteria for the OCTAVE Induction 1 and 2 and OCTAVE Sustain studies have been described previously. Briefly, eligible patients were ≥18 years of age, with a confirmed diagnosis of moderate to severe UC (total Mayo score of 6–12, with a rectal bleeding subscore of 1–3 and an endoscopic subscore of 2–3) for ≥4 months and had failed treatment with, or were intolerant to, at least 1 of the following: oral or intravenous corticosteroids, azathioprine or 6-
mercaptopyrurine, or tumor necrosis factor inhibitors (TNFis) (infliximab or adalimumab).

**Efficacy Assessments**

Efficacy assessments utilized the Mayo score. In the OCTAVE clinical program, any friability on the endoscopy subscore meant a scoring of ≥2. For definitions of remission, endoscopic improvement, and clinical response, see the Supplementary Methods.

Remission, endoscopic improvement, and clinical response were assessed at months 2 (centrally read endoscopy), 12, 24, and 36 (based on locally read endoscopic subscores) from baseline of the OCTAVE Open study (endoscopic readings in the OCTAVE Sustain study were centrally read).

PMS remission was defined as a PMS ≤2 with no individual subscore >1. PMS remission was assessed at various time points up to month 36 from baseline of the OCTAVE Open study.

**Safety Assessments**

During the course of treatment with tofacitinib 5 mg BID, safety outcomes were assessed, and the incidence and severity of adverse events (AEs), classified in the Medical Dictionary for Regulatory Activities, including AEs of special interest, were reported. See the Supplementary Methods for further details of AEs of special interest. Patients underwent a 4-week safety follow-up evaluation after the last dose of study medication.

**Statistical Analysis**

All data were analyzed descriptively. The full analysis set (FAS) was defined as all patients who received at least 1 dose of study drug in the OCTAVE Open study.

**What You Need to Know**

**Background**

We evaluated the effects of long-term treatment with tofacitinib—an oral, small molecule Janus kinase inhibitor in patient with ulcerative colitis.

**Findings**

Most patients who achieved remission after maintenance treatment with either tofacitinib 5 mg or 10 mg twice daily for 52 weeks maintained remission over 36 months with tofacitinib 5 mg twice daily in an open-label, long-term extension study.

**Implications for patient care**

Findings of the durability of efficacy with tofacitinib 5 mg twice daily supports its use in long-term maintenance therapy for patients with ulcerative colitis in remission after 52 weeks of maintenance therapy.

Efficacy outcomes were analyzed in the maintenance remission subpopulation (patients who had received tofacitinib 5 or 10 mg BID during the OCTAVE Sustain study) of the FAS. Nonresponder imputation (NRI) was applied after a patient discontinued the study or after the dose escalation, and last observation carried forward (LOCF) imputation was applied after a patient advanced to a subsequent study up to the visit they would have reached if they had remained in the study. No imputation for missing data was applied for ongoing patients, except NRI for intermittent missing data (NRI-LOCF). Observed case data are also presented. Data after the dose escalation were excluded for the observed case.

Safety was assessed in all patients who received at least 1 dose of tofacitinib 5 mg BID in the OCTAVE Open study, with no imputation for missing data.
All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patient Characteristics

At week 52 of the OCTAVE Sustain study, based on central endoscopic reading, 163 patients were in remission (maintenance remission subpopulation) and were assigned to receive tofacitinib 5 mg BID during the OCTAVE Open study. Of the OCTAVE Open maintenance remission subpopulation, 142 patients received tofacitinib 5 mg BID (n = 66) or tofacitinib 10 mg BID (n = 76) in the OCTAVE Sustain study (Figure 1). Twenty-one patients within the maintenance remission subpopulation received placebo during the OCTAVE Sustain study; these patients were included in the baseline demographics and clinical characteristics, and in the discontinuations, but were not included within the efficacy analyses. Twelve patients who were not in remission according to central endoscopic reading at entry into the OCTAVE Open study also received tofacitinib 5 mg BID but were not included in efficacy analyses presented here.

Baseline demographics and disease characteristics for patients in the maintenance remission subpopulation are presented in Table 1. At baseline of the OCTAVE Open study, 162 of 163 patients were not receiving concomitant corticosteroids. See the Supplementary Results for further information relating to concomitant corticosteroids.

Efficacy

The proportions of patients in the maintenance remission subpopulation achieving remission, endoscopic improvement, or clinical response during the OCTAVE Open study are shown in Figure 2. Observed data show that rates of remission and endoscopic improvement were generally maintained and broadly similar, irrespective of whether patients had received tofacitinib 5 or 10 mg BID during the OCTAVE Sustain study (Figure 2). PMS remission was maintained over time in the majority of patients, and rates were similar, irrespective of whether patients had received tofacitinib 5 or 10 mg BID during the OCTAVE Sustain study (Figure 3).

Ad hoc analysis of the maintenance of remission population showed that similar proportions of patients maintained remission or endoscopic improvement regardless of prior TNFi treatment status (Figure 2).

Within the maintenance remission subpopulation, 67 (41.1%) patients discontinued treatment in the OCTAVE Open study; see the Supplementary Results for further information relating to patient discontinuations.

Length of Time in Remission

Demographics and baseline characteristics were generally similar among patients in remission vs patients not in remission at month 12 of the OCTAVE Open study (Supplementary Table 1). Analysis of patients who reduced tofacitinib dose from 10 to 5 mg BID in the OCTAVE Open study, by duration of remission, shows that patients with a longer duration of remission in the OCTAVE Sustain study were more likely to stay in remission (Figure 4).

Dose Increase Due to Flare

Among the maintenance remission subpopulation, tofacitinib dose was increased from 5 to 10 mg BID due to flare in 41 patients, of whom 37 had received tofacitinib (14 patients received tofacitinib 5 mg BID and 23...
patients received tofacitinib 10 mg BID) during the OCTAVE Sustain study. Following dose escalation, 75.0% (n = 30 of 40), 77.4% (n = 24 of 31), 89.3% (n = 25 of 28), and 95.0% (n = 19 of 20) of patients achieved PMS remission at months 3, 6, 9, and 12, respectively (observed data). Corresponding NRI data were 73.2%
(n = 30 of 41), 58.5% (n = 24 of 41), 64.1% (n = 25 of 39), and 48.7% (n = 19 of 39), respectively (Supplementary Figure 2).

Safety

A total of 175 patients (163 patients in the maintenance of remission subpopulation [including the 142 patients who received tofacitinib during the OCTAVE Sustain study and 12 placebo-treated patients, all of whom entered the OCTAVE Open study in remission] and 12 patients receiving tofacitinib 5 mg BID as protocol deviations) were assigned to receive tofacitinib 5 mg BID in the OCTAVE Open study, of whom 86.9% reported treatment-emergent AEs (Table 2). The most frequently reported treatment-emergent AEs by preferred term were “nasopharyngitis” (reported in 38 [21.7%] patients) and “worsening of UC” (reported in 41 [23.4%] patients). AEs in the tofacitinib 5 mg BID subpopulation of OCTAVE Open showed no time-dependent increase when compared with safety data from OCTAVE Sustain study patients treated with tofacitinib 5 or 10 mg BID (Table 2). The majority of infections were mild or moderate.

In patients receiving tofacitinib 5 mg BID during the OCTAVE Open study, herpes zoster (HZ) (nonserious and serious) occurred in 11 patients with an incidence rate (IR) (unique patients with events per 100 patient-years of exposure) of 2.1 (95% confidence interval [CI], 1.1–3.8); 1 of these HZ events was reported as a serious AE. A total of 6 (3.4%) patients had serious infections (IR, 1.1; 95% CI 0.4–2.5); 5 (2.9%) patients had malignancy (excluding nonmelanoma skin cancer [NMSC]) events (IR, 1.0; 95% CI, 0.3–2.2), and 5 (2.9%) patients had NMSC events (IR, 1.0; 95% CI, 0.3–2.3). One patient had complicated appendicitis (adjudicated as a gastrointestinal perforation). Of note, there were no events of deep vein thrombosis, pulmonary embolism, or death in patients receiving tofacitinib 5 mg BID during the OCTAVE Open study. For further details on AEs, see the Supplementary Results.

In patients who required dose escalation due to flare, there was 1 case each of serious infection, HZ
Figure 4. Proportion of patients who maintained remission at month 12 of the OCTAVE Open study, by duration of remission. Data are shown for patients who achieved remission at week 52 of the OCTAVE Sustain study with tofacitinib 10 mg BID and then reduced to 5 mg BID in the OCTAVE Open study. Remission was defined as a total Mayo score \(\leq 2\) with no individual subscore >1, and a rectal bleeding subscore of 0. Remission status in the OCTAVE Sustain study was based on central read of endoscopy: <6 months prior to dose reduction was defined as remission at week 52, but not week 24, regardless of remission status at the OCTAVE Sustain study baseline; 6 to <12 months prior to dose reduction was defined as remission at both weeks 24 and 52, but not at the OCTAVE Sustain study baseline; \(\geq 12\) months prior to dose reduction was defined as remission at the OCTAVE Sustain study baseline, week 24, and week 52.

Discussion

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of UC. This report presents post hoc analysis of data from an OLE study of tofacitinib in a subpopulation of patients with moderate to severe UC meeting remission criteria following completion of the 52-week OCTAVE Sustain study, extending previous efficacy and safety findings by a further 36 months. Among patients who achieved remission during maintenance treatment, tofacitinib 5 mg BID demonstrated durability of efficacy, with the majority of patients maintaining remission over 36 months in the OCTAVE Open study, as evidenced across a range of endpoints including remission, endoscopic improvement, PMS remission, and clinical response. Rates of remission, endoscopic improvement, PMS remission, and clinical response were sustained over 36 months of treatment, regardless of whether patients had previously received tofacitinib 5 or 10 mg BID during maintenance treatment and regardless of their prior TNFi treatment status.

The maintenance of clinical response and clinical remission are historically important goals in the management of patients with UC. The OCTAVE study protocols were approved prior to the publication of the U.S. Food and Drug Administration guidance for clinical trial endpoints and incorporated a more stringent definition of remission (with the inclusion of a rectal bleeding subscore of 0) than that used in other studies. Rates of endoscopic improvement (defined as a Mayo endoscopic subscore of 0 or 1) in the current analysis generally reflected those of remission, suggesting the validity of this endpoint in clinical practice. The use of PMS remission, which may represent a more practical outcome measure, given its avoidance of endoscopy, was associated with slightly higher remission rates over 12 months.

Data reported here, in which a high proportion of patients who demonstrated a response following 8 weeks of tofacitinib treatment achieved and remained in remission following 3 years of treatment, are similar to those reported in patients with other UC treatments. Of note, there are limited data from head-to-head studies comparing long-term efficacy of approved agents, and primary outcome measures were different across studies, making direct comparisons difficult.

A high proportion of patients maintained remission following tofacitinib dose reduction from 10 mg BID in the OCTAVE Sustain study to 5 mg BID in the OCTAVE Open study. These open-label, uncontrolled data suggest that once remission has been achieved on tofacitinib 10 mg BID maintenance treatment, tofacitinib dose could be reduced while maintaining remission. The ad hoc analysis presented here showed that length of time in remission may require consideration prior to dose reduction; however, these analyses are limited by the small patient numbers.

The majority of patients who entered the OCTAVE Open study in remission and had their tofacitinib dose increased from 5 to 10 mg BID due to flare achieved PMS remission by month 3 postdose increase; however, these
post hoc analyses are limited by the small sample size. Owing to the protocol design, endoscopy data in these patients who dose escalated were not available within a 3-month window period.

The safety profile of tofacitinib 5 mg BID demonstrated no new safety risks associated with long-term exposure up to 36 months. Safety outcomes during the OCTAVE Open study were comparable to those of the OCTAVE Sustain study. Tofacitinib has been associated with an increased risk of HZ, but is not in cancer; PE, pulmonary embolism; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Patients with inflammatory bowel disease receiving thiopurines have been reported to be at increased risk of certain types of malignancy, including lymphoma and NMSC. Observational data have shown the risk of NMSC associated with thiopurines to continue following discontinuation. In the maintenance of remission subpopulation, 5 patients had malignancies (excluding NMSC), including 1 patient with diffuse large B cell lymphoma. All patients with malignancies had prior exposure to thiopurines or TNFis; this was also true for 4 of the 5 patients who had NMSC.

The remission status of patients completing the OCTAVE Sustain study was determined via central read endoscopy, whereas the OCTAVE Open study utilized local endoscopy readings. Interpretation of endoscopic findings by a local or central reader has the potential for discord between readings. During the OCTAVE Sustain study, the Tofacitinib 5 and 10 mg BID Treatment Groups in the OCTAVE Sustain Study.4

Table 2. Summary of Safety Outcomes in the Tofacitinib 5 mg BID Treatment Group in the OCTAVE Open Study and, for Comparison, the Tofacitinib 5 and 10 mg BID Treatment Groups in the OCTAVE Sustain Study

<table>
<thead>
<tr>
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<th>OCTAVE Open Studya</th>
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<tbody>
<tr>
<td></td>
<td>Tofacitinib</td>
<td>Tofacitinib</td>
<td>Tofacitinib</td>
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<tr>
<td></td>
<td>5 mg BID (n = 175)</td>
<td>5 mg BID (n = 198)</td>
<td>10 mg BID (n = 196)</td>
</tr>
<tr>
<td>Median duration of tofacitinib, d</td>
<td>1170</td>
<td>363.5</td>
<td>368</td>
</tr>
<tr>
<td>TEAEs</td>
<td>152 (86.9)</td>
<td>143 (72.2)</td>
<td>156 (79.6)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0.0), 0.0 (0.0–0.7)</td>
<td>0 (0.0), 0.0 (0.0–2.5)</td>
<td>0 (0.0), 0.0 (0.0–2.4)</td>
</tr>
<tr>
<td>SAEs</td>
<td>33 (18.9)</td>
<td>10 (5.1)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>20 (11.4)</td>
<td>14 (7.1)</td>
<td>15 (7.7)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>20 (11.4)</td>
<td>18 (9.1)</td>
<td>19 (9.7)</td>
</tr>
<tr>
<td>Infections</td>
<td>102 (58.3), 33.9 (27.6–41.1)</td>
<td>71 (35.9), 62.5 (48.9–78.9)</td>
<td>78 (39.8), 72.8 (57.6–90.9)</td>
</tr>
<tr>
<td>HZ (nonserious and serious)c</td>
<td>11 (6.3), 2.1 (1.1–3.8)</td>
<td>3 (1.5), 2.1 (0.4–6.0)</td>
<td>10 (5.1), 6.6 (3.2–12.2)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>6 (3.4), 1.1 (0.4–2.5)</td>
<td>2 (1.0), 1.4 (0.2–4.9)</td>
<td>1 (0.5), 0.6 (0.0–3.5)</td>
</tr>
<tr>
<td>Opportunistic infectionsde</td>
<td>4 (2.3), 0.8 (0.2–2.0)</td>
<td>2 (1.0), 1.4 (0.2–4.9)</td>
<td>4 (2.0), 2.6 (0.7–6.7)</td>
</tr>
<tr>
<td>Serious HZ</td>
<td>1 (0.6), 0.2 (0.0–1.1)</td>
<td>0 (0.0), 0.0 (0.0–2.5)</td>
<td>0 (0.0), 0.0 (0.0–2.4)</td>
</tr>
<tr>
<td>Malignancies (excluding NMSC)d</td>
<td>5 (2.9), 1.0 (0.3–2.2)</td>
<td>0 (0.0), 0.0 (0.0–2.5)</td>
<td>0 (0.0), 0.0 (0.0–2.4)</td>
</tr>
<tr>
<td>NMSCd</td>
<td>5 (2.9), 1.0 (0.3–2.3)</td>
<td>0 (0.0), 0.0 (0.0–2.5)</td>
<td>3 (1.5), 1.9 (0.4–5.6)</td>
</tr>
<tr>
<td>Gastrointestinal perforationsdf</td>
<td>1 (0.6), 0.2 (0.0–1.1)</td>
<td>0 (0.0), 0.0 (0.0–2.5)</td>
<td>0 (0.0), 0.0 (0.0–2.4)</td>
</tr>
<tr>
<td>MACEd</td>
<td>2 (1.1), 0.4 (0.1–1.4)</td>
<td>1 (0.5), 0.7 (0.0–3.8)</td>
<td>1 (0.5), 0.6 (0.0–3.5)</td>
</tr>
<tr>
<td>DVT</td>
<td>0 (0.0), 0.0 (0.0–0.7)</td>
<td>0 (0.0), 0.0 (0.0–2.5)</td>
<td>0 (0.0), 0.0 (0.0–2.4)</td>
</tr>
<tr>
<td>PE</td>
<td>0 (0.0), 0.0 (0.0–0.7)</td>
<td>0 (0.0), 0.0 (0.0–2.5)</td>
<td>0 (0.0), 0.0 (0.0–2.4)</td>
</tr>
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</table>

Values are n (%) or incidence rate (95% confidence interval), unless otherwise indicated. Incidence rate is defined as unique patients with events per 100 patient-years of exposure; associated 95% confidence intervals were obtained by the exact Poisson method.

AE, adverse event; BID, twice daily; DVT, deep vein thrombosis; HZ, herpes zoster; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; PE, pulmonary embolism; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

aData are reported as per the May 27, 2019, data cut.

According to Investigator’s assessment.

*Refer to the Supplementary Methods for preferred terms.

Per adjudication by specialist review committee.

Excludes tuberculosis and herpes zoster with 2 adjacent dermatomes.

Excludes preferred terms of pilonidal cyst, perirectal abscess, rectal abscess, anal abscess, perineal abscess, and any preferred terms using the term fistula.
study, both locally and centrally read endoscopies were performed, both of which demonstrated the efficacy of tofacitinib as maintenance therapy vs placebo. Overall, local and central endoscopy readings were consistent, although efficacy by local endoscopy was numerically higher than when assessed by central endoscopy.16 The OCTAVE Open study is an open-label study with no placebo group; this has the potential to introduce bias in endoscopy outcomes. The analyses presented here only focus on patients who were in remission at the end of the OCTAVE Sustain study and did not include those who may have had a clinical response and were not in remission. In conclusion, this post hoc analysis of data from the OCTAVE Open study demonstrated the durability of efficacy with tofacitinib 5 mg BID and supports long-term maintenance with tofacitinib 5 mg BID up to 36 months in patients who were in remission after 52 weeks of maintenance therapy. Efficacy rates were sustained over 36 months of treatment, regardless of whether patients had previously received tofacitinib 5 or 10 mg BID during maintenance treatment and regardless of their prior TNFi treatment status.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.10.004.

References


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Conflicts of Interest
These authors disclose the following: Jean-Frederic Colombel has acted as a consultant for AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Celtrion, Eli Lilly, EnteroMed, Ferring Pharmaceuticals, Genentech, Gilead, Janssen, MedImmune, Merck & Co, NexBio, Novartis, Otsuka Pharmaceutical Development and Commercialization, Pfizer, Protagonist, Second Genome, Seres Therapeutics, Shire, Takeda, and Theradiag; has received financial support for research from AbbVie, Genentech, Janssen; and has participated in speakers’ bureaus for AbbVie, Celgene, Ferring Pharmaceuticals, Genentech, and Takeda. Mark T. Osterman has acted as an advisor to AbbVie, Celgene, Janssen, Lycera, Merck & Co, Pfizer, Takeda, and UCB. Andrew J. Thorpe, Leonardo Salese, Chudy I. Nduaka, Haiying Zhang, Nervin Lawendy, Gary S. Friedman, Daniel Quirk, and Chinyu Su are employees and stockholders of Pfizer. Walter Reinisch has acted as a consultant for AstraZeneca, Boehringer Ingelheim, 500

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**Supplementary Methods**

**Dose Increase Due to Flare**

At or after month 2 of the OCTAVE Open study, patients experiencing a flare could dose escalate tofacitinib from 5 to 10 mg twice daily (BID). A flare was defined as an increase in total Mayo score of \( \geq 3 \) points from baseline of the OCTAVE Sustain study, accompanied by an increase in rectal bleeding and site-read endoscopic subscore of \( \geq 1 \) point, after a minimum of 8 weeks of treatment in the OCTAVE Open study. Patients who increased tofacitinib dose from 5 to 10 mg BID due to flare were excluded from the observed data efficacy analysis, but treated as nonresponder imputation (NRI) after dose escalation for NRI and last observation carried forward (NRI-LOCF) imputation data.

**Concomitant Medication**

Patients were permitted to use concomitant oral 5-aminosalicylates or sulfasalazine. Prohibited medications included azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, mycophenolate, tacrolimus, interferon, tumor necrosis factor inhibitors, intravenous or rectally administered corticosteroids, and natalizumab, vedolizumab, or other antiadhesion molecule therapy. Patients were permitted to use concomitant oral corticosteroids up to 25 mg/d during induction but had to undergo mandatory tapering during maintenance. If the patients entered the OCTAVE Open study on oral corticosteroids, tapering was mandatory.

If the patient was unable to tolerate tapering below 10 mg/d, corticosteroids were permitted if the dose did not exceed 10 mg/d. Once corticosteroid-free status was achieved, reinitiation of oral corticosteroid therapy above 10 mg/d was considered rescue therapy, and patients were required to discontinue from the study.

**Study Discontinuation**

Patients within the maintenance of remission cohort were required to withdraw from the study if they initiated a new therapy for ulcerative colitis (UC), underwent surgery for UC, or remained on corticosteroids exceeding 15 mg/d of prednisone or equivalent after month 3, or if there were any safety concerns.

**Mayo Score**

Efficacy assessments utilized the Mayo score, which ranges from 0 to 12 points and comprises 4 subscores (graded from 0 to 3): stool frequency, rectal bleeding, and mucosal appearance on endoscopy (centrally read), and physician global assessment. The partial Mayo score measures disease activity in UC without endoscopy, and ranges from 0 to 9 points. It comprises 3 subscores (graded from 0 to 3): stool frequency, rectal bleeding, and physician global assessment.

**Efficacy Endpoints**

Remission was defined as a total Mayo score \( \leq 2 \) with no individual subscore >1, and a rectal bleeding subscore of 0. Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1 (defined as mucosal healing in the OCTAVE study protocols. In the OCTAVE clinical program, any friability on the endoscopy subscore meant a scoring of \( \geq 2 \). Clinical response was defined as a decrease from induction study baseline total Mayo score of \( \geq 3 \) points and \( \geq 30\% \), plus a decrease in rectal bleeding subscore of \( \geq 1 \) point or an absolute rectal bleeding subscore of 0 or 1.

**Adverse Events of Special Interest**

Adverse events (AEs) of special interest included serious infection events (any infection AE that required the infection to be classified as a serious AE [SAE]), herpes zoster (HZ), malignancies (excluding non-melanoma skin cancer [NMSC]), NMSC, gastrointestinal perforations, and major adverse cardiovascular events. In order to harmonize and standardize endpoint assessment, opportunistic infections, major adverse cardiovascular events, malignancy, and gastrointestinal perforation events were based on adjudication by specialist review committees.

HZ AEs corresponded to the system organ class of infections and infestations; preferred terms included “Herpes zoster,” “Herpes zoster disseminated,” “Herpes zoster cutaneous disseminated,” “Ophthalmic Herpes zoster,” “Herpes zoster oticus,” “Genital Herpes zoster,” “Herpes zoster pharyngitis,” “Herpes zoster necrotizing retinopathy,” “Herpes zoster infection neurological,” “Herpes zoster meningitis,” “Herpes zoster meningomyelitis,” and “Herpes zoster meningoencephalitis.”

**Supplementary Results**

**Concomitant Corticosteroids**

One patient who was receiving prednisone 7.5 mg daily was enrolled into the OCTAVE Open study as a protocol deviation. One patient who was not receiving corticosteroids at baseline of the OCTAVE Open study received prednisone (20 mg/d) for 2 days (days 36 and 37) during the OCTAVE Open study. Neither of these patients met the criteria for patient withdrawal, and both continued to participate in the study.
Discontinuations

Within the maintenance remission subpopulation, 67 (41.1%) patients discontinued treatment in the OCTAVE Open study: 26 of 67 (38.8%) patients discontinued for study drug–related reasons, and 41 of 67 (61.2%) discontinued for nonstudy drug–related reasons. Of the patients who withdrew due to reasons related to the study drug, 15 (9.2%) discontinued due to insufficient clinical response, and 11 (6.7%) discontinued due to AEs (excluding worsening of UC). Of the 15 patients who discontinued due to insuffcient clinical response, 3 had received placebo during the OCTAVE Sustain study, 6 had received tofacitinib 5 mg BID, and 6 had received tofacitinib 10 mg BID. One patient who discontinued in the OCTAVE Open study was enrolled directly from the OCTAVE Induction study and assigned to tofacitinib 5 mg BID as a protocol deviation. Nonstudy drug–related reasons for study discontinuation included AEs (n = 5 of 41, 12.2%), patient no longer willing to participate (n = 16 of 41, 39.0%), protocol violation (n = 2 of 41, 4.9%), pregnancy (n = 2 of 41, 4.9%), and other reasons (n = 14 of 41, 34.1%) (including enrollment into postmarketing surveillance).

Safety

A total of 6 (3.4%) patients had serious infections; however, there was no specific clustering, with 1 event each of appendicitis, gastroenteritis norovirus, HZ, necrotizing fasciitis, pulmonary mycosis, and tonsillitis. Five patients who received tofacitinib 5 mg BID during the OCTAVE Open study had malignancy (excluding NMSC) events, including 1 event each of lung cancer, cervical dysplasia, and diffuse large B cell lymphoma, and 2 patients had breast cancer. All patients discontinued in the study, with the exception of the patient with cervical dysplasia. Three patients with malignancy events had prior immunosuppressant therapy use, and 2 had prior tumor necrosis factor inhibitor use.

Of the 11 patients with HZ, 3 patients had received tofacitinib 10 mg BID during the OCTAVE Sustain study, 4 patients had received tofacitinib 5 mg BID, and 4 patients had received placebo. Two patients discontinued the study due to HZ events, and 2 required temporary discontinuation of treatment; all other patients continued in the study and treatment was not interrupted. Five patients who received tofacitinib 5 mg BID during the OCTAVE Open study had NMSC events; 4 patients had prior immunosuppressant use, and 2 had prior tumor necrosis factor inhibitor use.

Three patients, all of whom had a history of NMSC, had multiple NMSC events during the OCTAVE Open study. One patient developed appendicitis on day 10 of the OCTAVE Open study, underwent an appendectomy, and was adjudicated as a gastrointestinal perforation. Tofacitinib was discontinued following this event, which was deemed unrelated to the study drug.

References

Supplementary Figure 1. Study design (overview of the phase 3 OCTAVE program). \(^a\)Final complete efficacy assessment at week 8 of 52. Treatment continued up to week 9 of 53. \(^b\)Clinical response in the OCTAVE Induction 1 and 2 studies was defined as a decrease from baseline total Mayo score of \(\geq 3\) points and \(\geq 30\%\), plus a decrease in rectal bleeding subscore of \(\geq 1\) point or an absolute rectal bleeding subscore of 0 or 1. \(^c\)Study A3921139 (OCTAVE Open study) is ongoing. \(^d\)Remission was defined as a total Mayo score \(\leq 2\) with no individual subscore \(>1\), and a rectal bleeding subscore of 0. In the OCTAVE Open study, 12 patients not in remission at OCTAVE Open study entry received tofacitinib 5 mg twice daily (BID) and 1 patient in remission at OCTAVE Open study entry received tofacitinib 10 mg BID as protocol deviations.

Supplementary Figure 2. Proportion of patients in the maintenance remission–dose escalation subpopulation with partial Mayo score (PMS) remission. PMS remission was defined as a PMS \(\leq 2\) with no individual subscore \(>1\). Error bars are exact binomial 90% confidence intervals (Clopper-Pearson method). Nonresponder imputation (NRI) was applied after a patient discontinued the study, and last observation carried forward (LOCF) imputation was applied after a patient advanced to a subsequent study up to the visit they would have reached if they had remained in the study. No imputation for missing data was applied for ongoing patients, except NRI for intermittent missing data (NRI-LOCF).
### Supplementary Table 1. Patient Characteristics by OCTAVE Open Study Month 12 Remission Status Among Patients Who Achieved Remission During OCTAVE Sustain Study

<table>
<thead>
<tr>
<th>OCTAVE Open Study Month 12 Remission Status (as Observed)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OCTAVE Sustain Study: Tofacitinib 10 mg BID</th>
<th>OCTAVE Sustain Study: Tofacitinib 5 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OCTAVE Sustain Study</strong></td>
<td>In Remission</td>
<td>Not in Remission</td>
</tr>
<tr>
<td>Male</td>
<td>25 (45)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Age at OCTAVE Induction study baseline, y</td>
<td>46.0 ± 14.8</td>
<td>42.4 ± 16.2</td>
</tr>
<tr>
<td>Total Mayo score at OCTAVE Induction study baseline</td>
<td>8.7 ± 1.6</td>
<td>8.0 ± 1.3</td>
</tr>
<tr>
<td>Endoscopic subscore at OCTAVE Open study baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (30)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>1</td>
<td>39 (70)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>CRP at OCTAVE Open study baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 mg/L</td>
<td>49/56 (88)</td>
<td>9/10 (90)</td>
</tr>
<tr>
<td>≥3 mg/L</td>
<td>7/56 (13)</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td>Extent of disease at OCTAVE Induction study baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctosigmoiditis</td>
<td>11/55 (20)</td>
<td>5/12 (42)</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>16/55 (29)</td>
<td>5/12 (42)</td>
</tr>
<tr>
<td>Extensive colitis/pancolitis</td>
<td>28/55 (51)</td>
<td>2/12 (17)</td>
</tr>
<tr>
<td>Prior TNFi failure at OCTAVE Induction study baseline</td>
<td>25 (45)</td>
<td>6 (50)</td>
</tr>
</tbody>
</table>

Values are n (%), mean ± SD, or n/n (%).

Remission was defined as a total Mayo score ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. PMS remission was defined as a PMS of ≤2 with no individual subscore >1.

BID, twice daily; CRP, C-reactive protein; PMS, partial Mayo score; TNFi, tumor necrosis factor inhibitor.

*Remission status in the OCTAVE Open study was based on local read of endoscopy.*

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<sup>a</sup> Remission status in the OCTAVE Open study was based on local read of endoscopy.
### Supplementary Table 2. Summary of Safety Outcomes in the Maintenance Remission-Dose Escalation Subpopulation of the OCTAVE Open Study

<table>
<thead>
<tr>
<th>Event</th>
<th>Tofacitinib Maintenance Remission-Dose Escalation Subpopulation (n = 41)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>40 (97.6)</td>
</tr>
<tr>
<td>SAEs&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Deaths&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0 (0.0), 0.0 (0.0–3.0)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1 (2.4), 0.8 (0.0–4.6)</td>
</tr>
<tr>
<td>HZ (nonserious and serious)</td>
<td>1 (2.4), 0.8 (0.0–4.6)</td>
</tr>
<tr>
<td>Opportunistic infections&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 (2.4), 0.8 (0.0–4.6)</td>
</tr>
<tr>
<td>Non-HZ opportunistic infections&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0 (0.0), 0.0 (0.0–3.0)</td>
</tr>
<tr>
<td>Malignancies (excluding NMSC)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>1 (2.4), 0.8 (0.0–4.6)</td>
</tr>
<tr>
<td>NMSC&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>3 (7.3), 2.6 (0.5–7.5)</td>
</tr>
<tr>
<td>MACE&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>0 (0.0), 0.0 (0.0–3.0)</td>
</tr>
<tr>
<td>DVT</td>
<td>0 (0.0), 0.0 (0.0–3.0)</td>
</tr>
<tr>
<td>PE</td>
<td>0 (0.0), 0.0 (0.0–3.0)</td>
</tr>
</tbody>
</table>

Values are n (%) or incidence rate (95% confidence interval).

Incidence rate is defined as unique patients with events per 100 patient-years of exposure; associated 95% confidence intervals were obtained by the exact Poisson method.

AE, adverse event; DVT, deep vein thrombosis; HZ, herpes zoster; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; PE, pulmonary embolism; SAE, serious adverse event.

<sup>a</sup>Data are reported as per the May 27, 2019, data cut.

<sup>b</sup>According to Investigator’s assessment.

<sup>c</sup>All events, including those that are outside the 28-day risk period, are included.

<sup>d</sup>Per adjudication by specialist review committee.