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# Persistence of treatment in patients with ulcerative colitis who responded to tofacitinib therapy: data from the open-label, long-term extension study, OCTAVE open

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## Summary

**Background:** Tofacitinib is an oral Janus kinase inhibitor for the treatment of ulcerative colitis (UC).

**Aim:** This post hoc analysis evaluated tofacitinib persistence in patients with UC in OCTAVE Open, an open-label, long-term extension study of patients receiving tofacitinib 5 or 10 mg twice daily.

**Methods:** Kaplan-Meier estimates for tofacitinib drug survival and reasons for discontinuations were evaluated. Baseline factors were analysed as predictors of persistence.

**Results:** This analysis included 603 patients: 280 entered OCTAVE Open with a clinical response (164 in remission and 116 not in remission), 220 were delayed responders, 75 were retreatment responders and 35 were dose escalation responders, treated for up to 7 years in OCTAVE Open. Of these, 118 (42.1%) responders, 121 (55.0%) delayed responders, 40 (53.3%) retreatment responders and 17 (48.6%) dose escalation responders discontinued tofacitinib with a median time to discontinuation of 5.6, 4.5, 4.0 and 4.4 years, respectively. The estimated 2- and 5-year drug survival rates in the responders (including patients in remission and not in remission) were 73.9% and 54.5%, respectively. Corresponding persistence values for delayed responders were 69.5% and 45.2%, for retreatment responders, 70.7% and 40.0%, and for dose escalation responders, 74.3% and 32.8%.

**Conclusion:** In OCTAVE Open, a high proportion of patients maintained tofacitinib treatment, with the median survival by group ranging from 4.0 to 5.6 years although these analyses are post hoc and limited by sample size. Further research should focus on factors to enhance persistence with tofacitinib treatment in patients with UC.

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## 1 | INTRODUCTION

Ulcerative colitis (UC) is a chronic, immune-mediated, idiopathic inflammatory bowel disease which is characterised by mucosal inflammation in the rectum and colon.[1,2] The primary goal of management of patients with moderate to severe UC is to achieve sustained steroid-free remission, improve quality of life, reduce morbidity and prevent disease complications and surgery.[2-4]

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of UC. The efficacy and safety of tofacitinib were demonstrated in a phase 2, double-blind, placebo-controlled, 8-week induction study (NCT00787202),[5] two identical phase 3, randomised, placebo-controlled, 8-week induction studies (OCTAVE Induction 1 and 2; NCT01465763 and NCT01458951) and a phase 3, randomised, placebo-controlled, 52-week maintenance study (OCTAVE Sustain; NCT01458574).[6] The long-term safety and efficacy of tofacitinib in patients with UC have been evaluated up to 7 years in a phase 3, multicentre, open-label, long-term extension study (OCTAVE Open; NCT01470612).[7] In OCTAVE Open, the safety profile of tofacitinib remained stable and efficacy was maintained with tofacitinib 5 and 10 mg b.d. up to 36 months.[7]

Time on treatment, also referred to as survival time, time to discontinuation, persistence or durability of treatment, is a surrogate measure of treatment success (effectiveness, tolerability and safety) in the long-term management of disease[8,9] and also represents a persistent response to a specific mode of action.

The objective of this post hoc analysis was to evaluate tofacitinib drug survival and persistence in OCTAVE Open, up to 7 years, across selected subgroups of patients with differing levels of disease activity at baseline OCTAVE Open and explore the reasons for treatment discontinuation, and to evaluate baseline clinical and demographic factors that may influence treatment persistence.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

These results are based on discontinuation data from selected subgroups in OCTAVE Open (NCT01470612). OCTAVE Open was a phase 3, multicentre, open-label, long-term extension study for patients who had previously enrolled in the phase 3 induction (OCTAVE Induction 1 and 2; NCT01465763 and NCT01458951) and/or maintenance (OCTAVE Sustain; NCT01458574) studies. OCTAVE Open was conducted between October 2012 to August 2020 (first patient first visit: October 1, 2012; last patient last visit: August 6, 2020); however, duration of treatment of individual patients varied depending on when they enrolled in the study and when the study completed. Therefore, the duration of participation for an individual patient may range from approximately 4 years up to 7 years. Full study design details for OCTAVE Induction 1 and 2, OCTAVE Sustain and OCTAVE Open have been reported previously.[6,7]

### 2.2 | Study populations

Analyses are presented for patients who enrolled into OCTAVE Open with or without a clinical response after participation in OCTAVE Induction 1 and 2, and OCTAVE Sustain (Figure 1).

Patients with a clinical response were analysed as three subpopulations: (1) all patients who had a clinical response at enrolment into OCTAVE Open (**all responders**); (2) patients who had a clinical response and were in remission (**responders in remission**), and were assigned to receive tofacitinib 5 mg twice daily (b.d.) per OCTAVE Open protocol and (3) patients who had a clinical response but were not in remission (**responders not in remission**), and were assigned to receive tofacitinib 10 mg b.d. per OCTAVE Open protocol (Figure 1).

Patients who enrolled into OCTAVE Open without a clinical response (non-responders) were analysed as three subpopulations: (1) **delayed responders**, defined as induction non-responders (patients who did not achieve a clinical response to 8 weeks' induction treatment with tofacitinib 10 mg b.d.) who achieved a clinical response at week 8 (total of 16 weeks' induction treatment) of OCTAVE Open and continued to receive tofacitinib 10 mg b.d. (Figure 1); (2) **retreatment responders**, defined as tofacitinib 10 mg b.d. induction responders who experienced treatment failure with placebo in OCTAVE Sustain and entered OCTAVE Open and received tofacitinib 10 mg b.d., and achieved a clinical response at week 8 of OCTAVE Open (Figure 1); and (3) **dose escalation responders,** defined as tofacitinib 10 mg b.d. induction responders who experienced treatment failure with tofacitinib 5 mg b.d. in OCTAVE Sustain and entered OCTAVE Open and received 10 mg b.d., and achieved a clinical response at week 8 of OCTAVE Open (Figure 1).

Tofacitinib dose adjustments were permitted in OCTAVE Open after at least 8 weeks of treatment in the trial, and multiple dose adjustments were allowed over the course of the study. For patients assigned to receive tofacitinib 5 mg b.d., the dose could be adjusted to 10 mg b.d. following loss of response documented by local read endoscopy. For patients assigned to receive tofacitinib 10 mg b.d., tofacitinib dose could be adjusted to 5 mg b.d. if the patients met

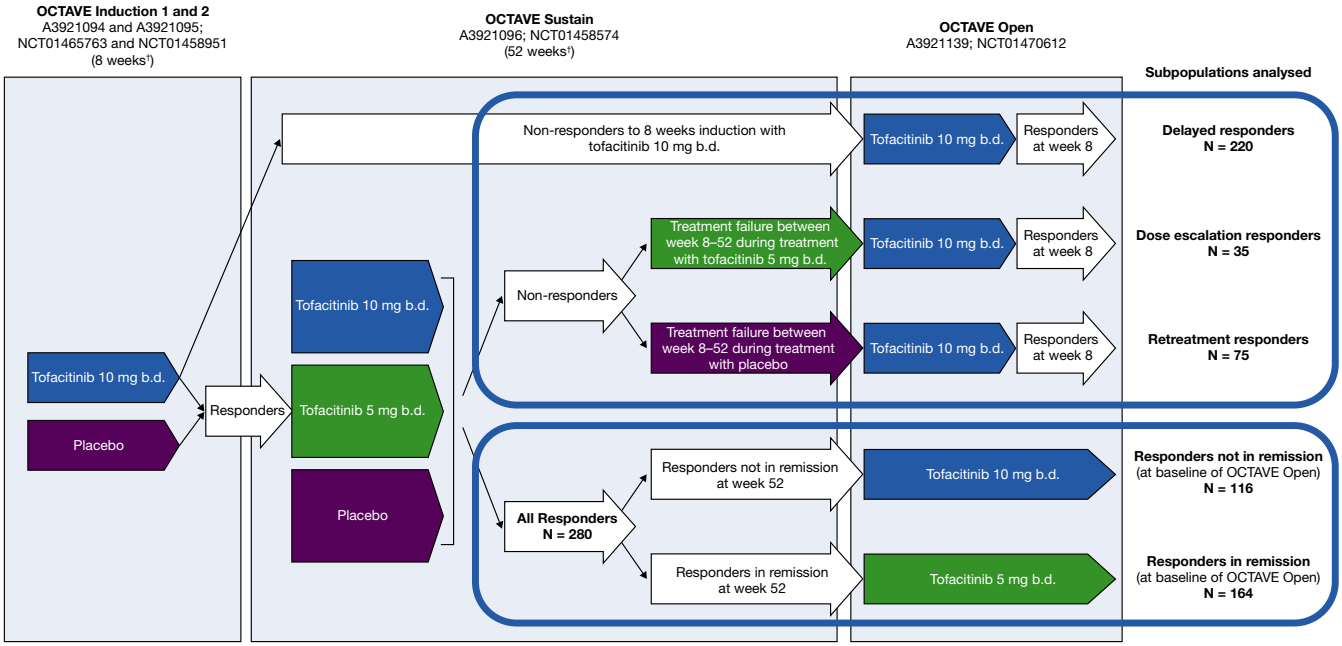



**FIGURE 1** Overview of the tofacitinib treatment sequences for patients in the responder subpopulation including responders not in remission and responders in remission, the delayed responder subpopulation, the retreatment responder subpopulation and the dose escalation responder subpopulation. Clinical response was defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, with a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1. Remission was defined as a total Mayo score of ≤2, with no individual subscore >1 and a rectal bleeding subscore of 0. Treatment failure was defined as an increase from OCTAVE Sustain baseline total Mayo score of ≥3 points, plus an increase in rectal bleeding subscore and endoscopic subscore of ≥1 point, and an absolute endoscopic subscore ≥2 after at least 8 weeks of maintenance therapy. Retreatment responders and dose escalation responders had received tofacitinib 10 mg b.d. during OCTAVE Induction 1or 2 and demonstrated a clinical response at the end of the induction studies, but experienced treatment failure during OCTAVE Sustain. b.d., twice daily; *N*, number of patients treated. †Final complete efficacy assessment at week 8/52. Treatment continued up to week 9/53

any of the following laboratory criteria (repeated and confirmed within 7 days): any single haemoglobin value that dropped >2 g/dL below baseline of OCTAVE Open; an absolute neutrophil count <1200 neutrophils/mm$^3$; an absolute lymphocyte count <750 lymphocytes/mm$^3$; a platelet count <100,000 platelets/mm$^3$. In addition, for patients receiving tofacitinib 10 mg b.d., the dose could be adjusted to 5 mg b.d. if the patient was in remission (based on total Mayo score) or in partial Mayo score (PMS) remission (defined as a PMS ≤2 with no individual subscore >1) at month 24 or at any visit beyond month 24, after discussion with the sponsor.

Furthermore, treatment interruption of any dose level was permitted for a period of up to 5 days (to treat a non-serious infection or other medical condition) once during OCTAVE Open. Treatment interruption for periods longer than 5 days for a medical reason required sponsor approval.

In OCTAVE Open, concomitant oral 5-aminosalicylates or sulfasalazine and corticosteroids were permitted. Corticosteroid tapering was mandatory at the beginning of OCTAVE Open, although if a patient could not tolerate tapering below 10 mg/day they were permitted to remain in the study provided their dose did not exceed 10 mg/day.

This study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines, and was approved by the Institutional Review Boards and/or Independent Ethics Committees at each investigational centre, or a central Institutional Review Board. All patients provided written informed consent. All authors had access to the study data and reviewed and approved the final manuscript. OCTAVE Open is registered at ClinicalTrials.gov: NCT01470612.

## 2.3 | Definitions

A **clinical response** was defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1. **Remission** was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0 (based on central read of the Mayo endoscopic subscore). **Treatment failure** was defined as an increase from OCTAVE Sustain baseline total Mayo score of ≥3 points, plus an increase in rectal bleeding subscore and endoscopic subscore of ≥1 point, and an absolute endoscopic subscore ≥2 after at least 8 weeks of maintenance therapy.

## 2.4 | Outcomes and statistical analysis

For each patient subpopulation, baseline values were obtained from the induction studies (OCTAVE Induction 1 and 2).

Persistence of treatment was the outcome of interest in this analysis. Persistence was defined as the number of days from the initial dosing in OCTAVE Open to the treatment discontinuation date plus 1 day. Persistence was censored at the date of treatment discontinuation for study completers, those enrolling into RIVETING (NCT03281304; an ongoing, randomised, parallel-group study designed to evaluate the efficacy and safety of tofacitinib dose reduction to 5 mg b.d vs remaining on 10 mg b.d in patients with UC who were in stable remission on tofacitinib 10 mg b.d.) or the Japan post-marketing study, or patients who were required to discontinue participation in OCTAVE Open following regulatory approval in Japan. In general, categorical data are presented descriptively (number, %).

Kaplan-Meier methodology was used to estimate the median drug persistence (years) in each of the subpopulations. Drug survival rates, with 95% CI, at 2 and 5 years were also estimated for each of the subpopulations.

Dose adjustments and dose interruptions were summarised. In the analysis presented here, the first dose adjustments, which lasted for at least 14 days, were considered, and doses may have varied subsequently. A dose interruption was defined as being without treatment for at least 1 day.

Cox proportional hazards models were used to explore the potential effects of induction baseline variables on risk of treatment discontinuation. This type of analysis was performed on all subpopulations combined. The models evaluated the following covariates: induction study baseline age category (<40 vs ≥40 years), albumin category (<3.5 g/dL vs ≥3.5 g/dL), C-reactive protein category (<3 mg/L vs ≥3 mg/L), disease duration (<6 vs ≥6 years), endoscopic score category (2 vs 3), extent of disease (proctosigmoiditis, left-sided colitis, extensive colitis/pancolitis, proctitis), prior hospitalisation (yes vs no), prior tumour necrosis factor inhibitor (TNFi) failure (yes vs no), gender (female vs male), oral corticosteroid

**TABLE 1** Induction baseline demographics and disease characteristics of patients in the subpopulations of OCTAVE Open

| | Responders in remission (*N* = 164)[a] | Responders not in remission (*N* = 116)[b] | All responders (*N* = 280)[c] | Delayed responders (*N* = 220)[d] | Retreatment responders (*N* = 75)[e] | Dose escalation responders (*N* = 35)[f] |
|---|---|---|---|---|---|---|
| Male, *n* (%) | 89 (54.3) | 71 (61.2) | 160 (57.1) | 130 (59.1) | 46 (61.3) | 14 (40.0) |
| Age, years, mean (SD) | 44.6 (14.8) | 42.7 (12.8) | 43.8 (14.0) | 40.8 (13.7) | 46.1 (13.3) | 41.2 (12.0) |
| BMI, kg/m$^2$, mean (SD) | 25.7 (4.8) | 24.9 (4.9) | 25.3 (4.8) | 24.2 (4.7) | 26.4 (4.8) | 24.4 (5.7) |
| Extent of disease, *n* (%) | | | | | | |
| Proctosigmoiditis | 34 (20.9)[g] | 12 (10.3)[h] | 46 (16.5) | 33 (15.0) | 4 (5.3) | 6 (17.1) |
| Left-sided colitis | 53 (32.5)[g] | 34 (29.3)[h] | 87 (31.2) | 75 (34.1) | 32 (42.7) | 13 (37.1) |
| Extensive colitis/pancolitis | 76 (46.6)[g] | 70 (60.3)[h] | 146 (52.3) | 112 (50.9) | 38 (50.7) | 16 (45.7) |
| Proctitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Disease duration, *n* (%) | | | | | | |
| <6 years | 87 (53.0) | 52 (44.8) | 139 (49.6) | 98 (44.5) | 31 (41.3) | 16 (45.7) |
| ≥6 years | 77 (47.0) | 64 (55.2) | 141 (50.4) | 122 (55.5) | 44 (58.7) | 19 (54.3) |
| Treatment history, *n* (%) | | | | | | |
| Prior TNFi use | 71 (43.3) | 54 (46.6) | 125 (44.6) | 129 (58.6) | 37 (49.3) | 19 (54.3) |
| Prior TNFi failure | 64 (39.0) | 52 (44.8) | 116 (41.4) | 126 (57.3) | 37 (49.3) | 17 (48.6) |
| Prior immunosuppressant use | 107 (65.2) | 93 (80.2) | 200 (71.4) | 175 (79.5) | 56 (74.7) | 32 (91.4) |
| Prior immunosuppressant failure | 101 (61.6) | 89 (76.7) | 190 (67.9) | 169 (76.8) | 54 (72.0) | 31 (88.6) |
| Oral corticosteroid use, *n* (%) | 64 (39.0) | 48 (41.4) | 112 (40.0) | 84 (38.2) | 28 (37.3) | 24 (68.6) |
| Prior hospitalisation, *n* (%) | | | | | | |
| Yes | 87 (53.0) | 68 (58.6) | 155 (55.4) | 121 (55.8)[i] | 42 (56.0) | 19 (54.3) |
| No | 74 (45.1) | 46 (39.7) | 120 (42.9) | 94 (43.3)[i] | 32 (42.7) | 15 (42.9) |
| Unknown | 3 (1.8) | 2 (1.7) | 5 (1.8) | 2 (0.9)[i] | 1 (1.3) | 1 (2.9) |
| Baseline albumin, *n* (%) | | | | | | |
| <3.5 g/dL | 6 (3.7) | 5 (4.3) | 11 (3.9) | 10 (4.5) | 3 (4.0) | 3 (8.6) |
| ≥3.5 g/dL | 158 (96.3) | 111 (95.7) | 269 (96.1) | 210 (95.5) | 72 (96.0) | 32 (91.4) |
| Baseline C-reactive protein, *n* (%) | | | | | | |
| <3 mg/L | 74 (46.0)[j] | 40 (35.1)[k] | 114 (41.5)[l] | 82 (37.6)[m] | 21 (28.0) | 17 (48.6) |
| ≥3 mg/L | 87 (54.0)[j] | 74 (64.9)[k] | 161 (58.5)[l] | 136 (62.4)[m] | 54 (72.0) | 18 (51.4) |

TABLE 1 (Continued)

| | Responders in remission (*N* = 164)[a] | Responders not in remission (*N* = 116)[b] | All responders (*N* = 280)[c] | Delayed responders (*N* = 220)[d] | Retreatment responders (*N* = 75)[e] | Dose escalation responders (*N* = 35)[f] |
|---|---|---|---|---|---|---|
| Endoscopic subscore,[n] *n* (%) | | | | | | |
| 2 | 81 (49.4) | 39 (33.6) | 120 (42.9) | 85 (38.6) | 34 (45.3) | 15 (42.9) |
| 3 | 83 (50.6) | 77 (66.4) | 160 (57.1) | 135 (61.4) | 41 (54.7) | 20 (57.1) |

*Note*: Seven patients met the criteria for responders not in remission and either the retreatment responders or dose escalation responders after maintenance failure criteria, simultaneously. These patients are only counted once overall (*N* = 603).

Abbreviations: b.d., twice daily; BMI, body mass index; *n*, number of patients in a given category; *N*, number of patients in the analysis population; SD, standard deviation; TNFi, tumour necrosis factor inhibitor.

[a]Patients with a clinical response and in remission at baseline of OCTAVE Open; 163 patients were assigned to receive tofacitinib 5 mg b.d. and 1 patient (protocol deviation) was assigned to receive tofacitinib 10 mg b.d. in OCTAVE Open.

[b]Patients with a clinical response but not in remission at baseline of OCTAVE Open; 11 patients (protocol deviations) were assigned to receive tofacitinib 5 mg b.d. and 105 patients were assigned to receive tofacitinib 10 mg b.d. in OCTAVE Open.

[c]All patients with a clinical response (including responders/remitters and responders/non-remitters) at baseline of OCTAVE Open; 174 patients were assigned to receive tofacitinib 5 mg b.d. and 106 patients were assigned to receive tofacitinib 10 mg b.d. in OCTAVE Open.

[d]Induction non-responders (patients who received tofacitinib 10 mg b.d. in OCTAVE Induction 1 and 2 and failed to demonstrate a clinical response at week 8, and subsequently enrolled into OCTAVE Open to receive tofacitinib 10 mg b.d. for an additional 8 weeks) who achieved a clinical response at month 2 of OCTAVE Open.

[e]Induction responders (patients who received tofacitinib 10 mg b.d. in OCTAVE Induction 1 and 2, and demonstrated a clinical response at week 8) who subsequently enrolled into OCTAVE Sustain to receive placebo and experienced treatment failure, and subsequently enrolled into OCTAVE Open to receive tofacitinib 10 mg b.d. and achieved a clinical response at month 2 of OCTAVE Open.

[f]Induction responders who subsequently enrolled into OCTAVE Sustain to receive tofacitinib 5 mg b.d. and experienced treatment failure, and dose escalated to tofacitinib 10 mg b.d. in OCTAVE Open and achieved a clinical response at month 2 of OCTAVE Open; 2 patients (protocol deviations) were assigned to receive tofacitinib 5 mg b.d. and 33 patients were assigned to receive tofacitinib 10 mg b.d. in OCTAVE Open.

[g]*N* = 163.

[h]*N* = 279.

[i]*N* = 217.

[j]*N* = 161.

[k]*N* = 114.

[l]*N* = 275.

[m]*N* = 218.

[n]Data are from baseline of OCTAVE Open; central read.

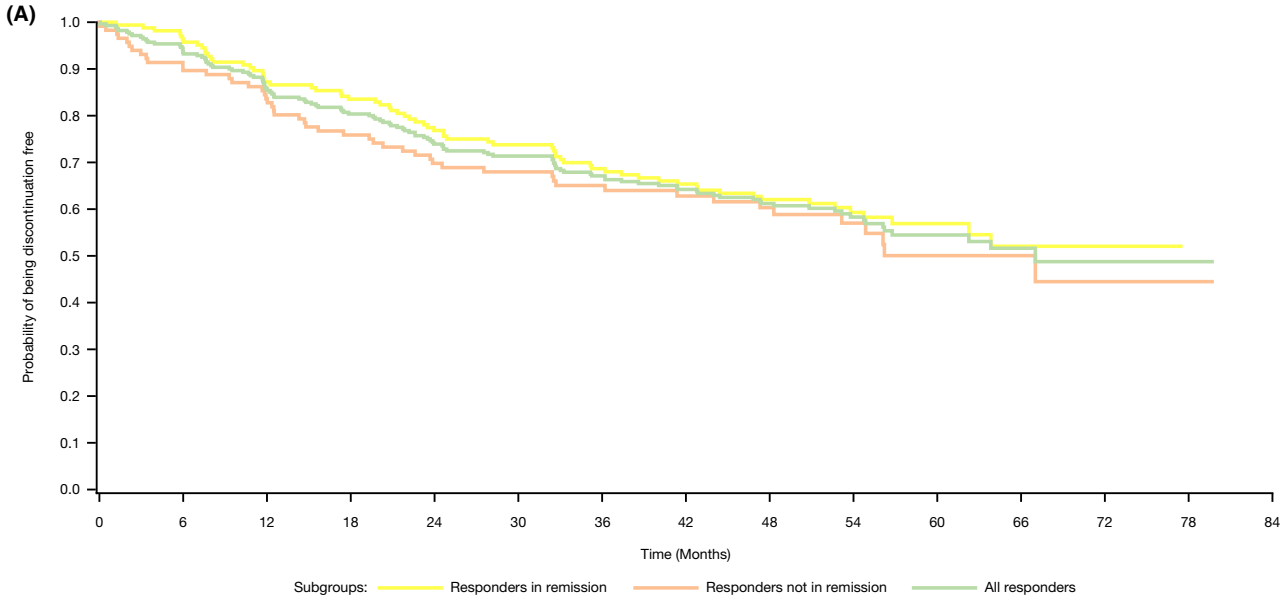
use at baseline (yes vs no) and tofacitinib dose in OCTAVE Open (10 mg b.d. vs 5 mg b.d.). These covariates were chosen for testing because of their presumed association with increased risk of drop-out. Backwards selection with *p*-value for retaining variables in the model of 0.15 was implemented to arrive at the final multivariate model. The hazard ratios, 95% CI and *p*-values from the final model are presented. Cox proportional hazards analyses were conducted where the event of interest was treatment discontinuation due to any reason and separately for events of discontinuation due to insufficient clinical response.

## 3 | RESULTS

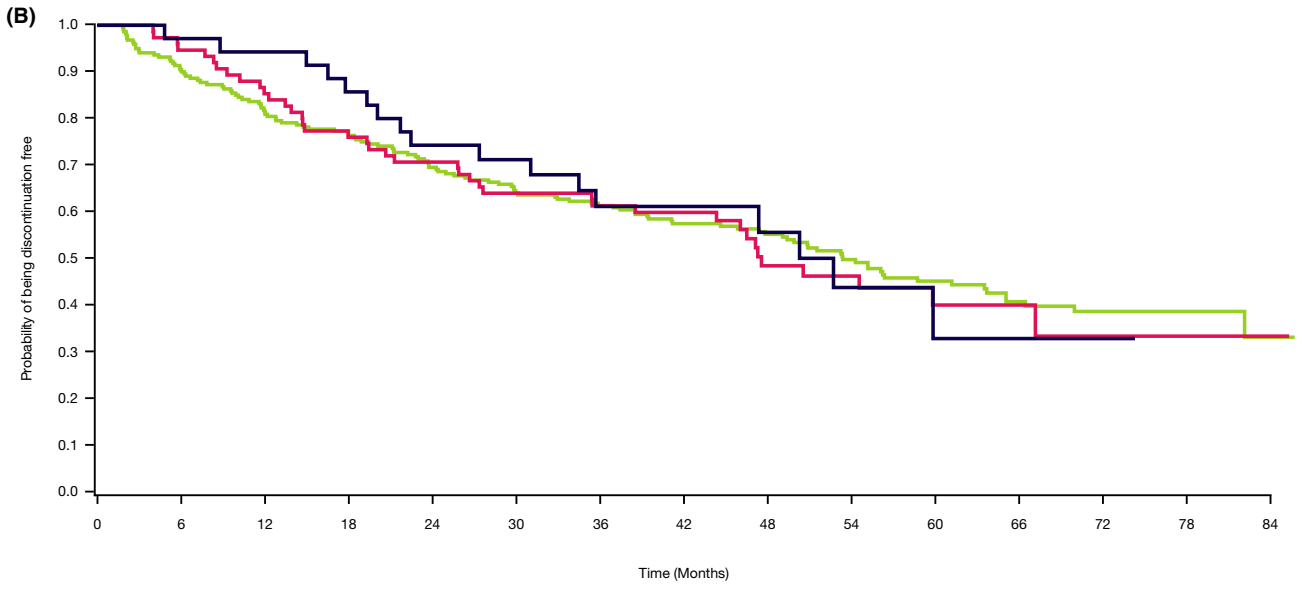
### 3.1 | Patients

This analysis included 603 patients, of which 280 were responders at baseline at OCTAVE Open (including 164 responders in remission and 116 responders not in remission), 220 were delayed responders, 75 were retreatment responders and 35 were dose escalation responders (Table 1). Seven patients met the criteria for responders not in remission and either the retreatment responders or dose escalation responders after maintenance failure criteria, simultaneously, and these patients are only counted once overall in the Cox proportional hazards analyses. Patient demographics and disease characteristics at baseline of the induction studies across patient subpopulations were largely comparable. However, the proportion of patients with prior TNFi failure and prior immunosuppressant failure were highest among the non-responder subpopulations (delayed responders, retreatment responders and dose escalation responders) vs responders (Table 1).

Patient demographics and disease characteristics were generally similar between responders in remission and responders not in remission at baseline of the induction studies, although compared with responders not in remission, a higher proportion of responders in remission had proctosigmoiditis, and a lower proportion of responders in remission had prior TNFi failure and immunosuppressant failure (Table 1). Compared with responders in remission, a higher proportion of responders not in remission had extensive colitis/pancolitis at baseline of the induction studies.




| Subpopulation | Month 6 | | Month 12 | | Month 18 | | Month 24 | | Month 30 | | Month 36 | | Month 42 | | Month 48 | | Month 54 | | Month 60 | | Month 66 | | Month 72 | | Month 78 | | Month 84 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events |
| Responders in remission | 158 | 6 | 143 | 21 | 137 | 27 | 126 | 38 | 117 | 43 | 105 | 51 | 99 | 56 | 90 | 61 | 57 | 64 | 31 | 66 | 10 | 68 | 3 | 68 | 0 | 68 | 0 | 68 |
| Responders not in remission | 104 | 12 | 97 | 19 | 88 | 28 | 77 | 35 | 71 | 37 | 62 | 40 | 53 | 42 | 41 | 44 | 27 | 46 | 16 | 49 | 10 | 49 | 5 | 50 | 1 | 50 | 0 | 50 |
| All responders | 262 | 18 | 240 | 40 | 225 | 55 | 203 | 73 | 188 | 80 | 167 | 91 | 152 | 98 | 131 | 105 | 84 | 110 | 47 | 115 | 20 | 117 | 8 | 118 | 1 | 118 | 0 | 118 |




| Subpopulation | Month 6 | | Month 12 | | Month 18 | | Month 24 | | Month 30 | | Month 36 | | Month 42 | | Month 48 | | Month 54 | | Month 60 | | Month 66 | | Month 72 | | Month 78 | | Month 84 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events | At risk | Events |
| Delayed responders | 199 | 21 | 179 | 41 | 170 | 50 | 153 | 67 | 141 | 79 | 133 | 85 | 109 | 93 | 95 | 97 | 78 | 106 | 59 | 113 | 42 | 118 | 18 | 120 | 10 | 120 | 1 | 121 |
| Retreatment responders | 71 | 4 | 64 | 11 | 57 | 18 | 53 | 22 | 48 | 27 | 44 | 29 | 37 | 30 | 24 | 36 | 19 | 37 | 11 | 39 | 6 | 39 | 3 | 40 | 1 | 40 | 1 | 40 |
| Dose escalation responders | 34 | 1 | 33 | 2 | 30 | 5 | 25 | 9 | 23 | 10 | 18 | 13 | 14 | 13 | 10 | 14 | 7 | 16 | 3 | 17 | 2 | 17 | 1 | 17 | 0 | 17 | 0 | 17 |

**FIGURE 2** Kaplan-Meier drug survival estimates for (A) all responders, responders in remission and responders not in remission, and (B) delayed responders, retreatment responders and dose escalation responders. Drug survival was calculated in days as the time from the first dose in OCTAVE Open to the date of treatment discontinuation plus 1 day. Persistence of treatment was censored as the date of treatment discontinuation for patients meeting censoring criteria. Responders included responders in remission and responders not in remission

At baseline of the induction studies, patient demographics and disease characteristics were generally similar across delayed responders, retreatment responders and dose escalation responders (Table 1). Compared with delayed responders and retreatment responders, a lower proportion of dose escalation responders were male, and compared with delayed responders and dose escalation responders, a lower proportion of retreatment responders had proctosigmoiditis. A higher proportion of dose escalation responders had prior immunosuppressant use and failure, compared with delayed responders and retreatment responders. The proportion of patients with TNFi failure was highest among delayed responders compared with retreatment responders and dose escalation responders.

## 3.2 | Dose adjustments and interruptions

During OCTAVE Open, the majority of responder patients remained on the tofacitinib dose assigned at baseline; however, when considering the first dose adjustment, lasting at least 14 days, 43/164 (26.2%) responders in remission increased tofacitinib dose from 5 mg b.d. to 10 mg b.d. and 15/116 (12.9%) responders not in remission decreased tofacitinib dose from 10 mg b.d. to 5 mg b.d.

The majority of delayed responder patients continued to receive tofacitinib 10 mg b.d. during OCTAVE Open, although 51/220 (23.2%) patients had a dose reduction to 5 mg b.d. Similarly, 15/75 (20.0%) retreatment responders and 5/35 (14.3%) dose escalation responders reduced their tofacitinib dose from 10 mg b.d. to 5 mg b.d. during OCTAVE Open. These dose adjustments refer to the initial change from OCTAVE Open baseline dose which lasted at least 14 days. Dose levels may have varied subsequently.

Overall, 286/603 (47.4%) patients had a dose interruption of at least 1 day. Although multiple dose interruptions of at least 1 day were observed (data not shown); the median maximum duration of interruption per patient was 5 days, as required by the protocol, and was generally similar across the subpopulations (Table S1).

## 3.3 | Tofacitinib persistence

Median tofacitinib persistence for all responder patients was 5.6 years. Among all responders, estimated 2- and 5-year drug persistence rates were 73.9% and 54.5%, respectively (Figure 2). Estimated 2- and 5-year drug survival rates were numerically higher among responders in remission (76.8% and 56.9%, respectively) compared with the responders not in remission (69.8% and 50.0%, respectively) (Figure 2).

Median tofacitinib persistence was comparable for delayed responders, retreatment responders and dose escalation responders (4.5, 4.0 and 4.4 years, respectively). The estimated 2- and 5-year drug persistence rates in delayed responders were 69.5% and 45.2%, respectively (Figure 2). Corresponding values for retreatment responders were 70.7% and 40.0%, and for dose escalation responders, 74.3% and 32.8%, respectively (Figure 2).

Cox proportional hazards models were fitted to evaluate potential predictors of discontinuation from treatment in OCTAVE Open and it was found that for discontinuations due to any reason, younger age (<40 years), being female and tofacitinib dose of 10 mg b.d. at OCTAVE Open baseline, were associated with increased risk of discontinuation (Table 2). Albumin category, C-reactive protein category, disease duration, endoscopic score category, extent of disease, prior hospitalisation, prior TNFi failure and oral corticosteroid use at baseline, were not significant predictors of discontinuation. In a similar analysis to evaluate potential predictors of discontinuation from treatment in OCTAVE Open due to insufficient clinical response, it was found that younger age (<40 years), tofacitinib dose of 10 mg b.d. at OCTAVE Open baseline and prior TNFi failure were associated with increased risk of discontinuation (Table 2).

**TABLE 2** Predictors of treatment discontinuation: Cox proportional hazards regression analysis[a]

| Predictor variable | Comparison | Hazard ratio (95% CI) | *p*-value |
|---|---|---|---|
| Event: Discontinuation for any reason | | | |
| Age category at induction baseline | <40 vs ≥40 years | 1.48 (1.18–1.87) | 0.0008 |
| Tofacitinib dose in OCTAVE Open | 10 vs 5 mg b.d. | 1.33 (1.02–1.73) | 0.0380 |
| Gender | Female vs male | 1.30 (1.03–1.64) | 0.0256 |
| Event: Discontinuation due to insufficient clinical response | | | |
| Age category at induction baseline | <40 vs ≥40 years | 1.65 (1.15–2.36) | 0.0067 |
| Prior TNFi failure | Yes vs no | 1.62 (1.12–2.35) | 0.0105 |
| Tofacitinib dose in OCTAVE Open | 10 vs 5 mg b.d. | 2.01 (1.24–3.26) | 0.0047 |

*Note*: Backward elimination with *p*-value stay criterion of 0.15 was used to arrive at the final model. The covariate tested were induction study baseline age category, albumin category, C-reactive protein category, disease duration, endoscopic score category, extent of disease, prior hospitalisation, prior TNFi failure, gender and oral corticosteroid use at baseline.

Abbreviations: b.d., twice daily; CI, confidence interval; TNFi, tumour necrosis factor inhibitor.

[a]Analyses conducted in 603 patients with 292 discontinuation events for any reason and 120 discontinuations due to insufficient clinical response.

### 3.4 | Reasons for tofacitinib discontinuation

Overall, 118/280 (42.1%) responders discontinued tofacitinib treatment early (ie did not discontinue OCTAVE Open due to enrolment into RIVETING or the Japan post-marketing study, or following regulatory approval in Japan) during OCTAVE Open, including 68/164 (41.5%) responders in remission and 50/116 (43.1%) responders not in remission (Table 3). Compared with responders, a numerically higher proportion of delayed responders, retreatment responders and dose escalation responders, 121/220 (55.0%), 40/75 (53.3%) and 17/35 (48.6%), respectively, discontinued tofacitinib treatment early during OCTAVE Open. These early discontinuations were considered as events in the Kaplan-Meier and Cox proportional hazards analyses of persistence.

The most common reasons for discontinuations across all subpopulations were insufficient clinical response, lack of patient

**TABLE 3** Reasons for study discontinuation in the subpopulations of OCTAVE Open

| *n* (%) | Responders in remission (*N* = 164)[a] | Responders not in remission (*N* = 116)[b] | All responders (*N* = 280)[c] | Delayed responders (*N* = 220)[d] | Retreatment responders (*N* = 75)[e] | Dose escalation responders (*N* = 35)[f] |
|---|---|---|---|---|---|---|
| Adverse event | | | | | | |
| Related to study drug | 12 (7.3) | 4 (3.4) | 16 (5.7) | 21 (9.5) | 3 (4.0) | 0 (0.0) |
| Not related to study drug | 8 (4.9) | 6 (5.2) | 14 (5.0) | 10 (4.5) | 9 (12.0) | 0 (0.0) |
| Insufficient clinical response | 20 (12.2) | 20 (17.2) | 40 (14.3) | 56 (25.5) | 16 (21.3) | 11 (31.4) |
| Did not meet OCTAVE Open inclusion criteria | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| No longer willing to participate | 19 (11.6) | 16. (13.8) | 35 (12.5) | 22 (10.0) | 8 (10.7) | 2 (5.7) |
| Lost to follow-up | 2 (1.2) | 1 (0.9) | 3 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Protocol violation | 2 (1.2) | 0 (0.0) | 2 (0.7) | 3 (1.4) | 0 (0.0) | 2 (5.7) |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Withdrawn because of pregnancy | 2 (1.2) | 2 (1.7) | 4 (1.4) | 3 (1.4) | 1 (1.3) | 1 (2.9) |
| Other[g] | 3 (1.8) | 1 (0.9) | 4 (1.4) | 6 (2.7) | 1 (1.3) | 1 (2.9) |
| Early tofacitinib discontinuation[h] | 68 (41.5) | 50 (43.1) | 118 (42.1) | 121 (55.0) | 40 (53.3) | 17 (48.6) |
| Other (censored) | | | | | | |
| Enrolled into RIVETING[i] | 3 (1.8) | 36 (31.0) | 39 (13.9) | 45 (20.5) | 20 (26.7) | 12 (34.3) |
| Enrolled into PMS (Japan only) | 8 (4.9) | 0 (0.0) | 8 (2.9) | 1 (0.5) | 2 (2.7) | 1 (2.9) |
| Regulatory approval in Japan[j] | 1 (0.6) | 2 (1.7) | 3 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Total study discontinuations | 80 (48.8) | 88 (75.9) | 168 (60.0) | 167 (75.9) | 62 (82.7) | 30 (85.7) |

Abbreviations: b.d., twice daily; *n*, number of patients in a given category; *N*, number of patients in the analysis population; PMS, post-marketing surveillance.

[a]Patients with a clinical response and in remission at baseline of OCTAVE Open; 163 patients were assigned to receive tofacitinib 5 mg b.d. and 1 patient (protocol deviation) was assigned to receive tofacitinib 10 mg b.d. in OCTAVE Open.

[b]Patients with a clinical response but not in remission at baseline of OCTAVE Open; 11 patients (protocol deviations) were assigned to receive tofacitinib 5 mg b.d. and 105 patients were assigned to receive tofacitinib 10 mg b.d. in OCTAVE Open.

[c]All patients with a clinical response (including responders/remitters and responders/non-remitters) at baseline of OCTAVE Open; 174 patients were assigned to receive tofacitinib 5 mg b.d. and 106 patients were assigned to receive tofacitinib 10 mg b.d. in OCTAVE Open.

[d]Induction non-responders (patients who received tofacitinib 10 mg b.d. in OCTAVE Induction 1 and 2 and failed to demonstrate a clinical response at week 8, and subsequently enrolled into OCTAVE Open to receive tofacitinib 10 mg b.d. for an additional 8 weeks) who achieved a clinical response at month 2 of OCTAVE Open.

[e]Induction responders (patients who received tofacitinib 10 mg b.d. in OCTAVE Induction 1 and 2, and demonstrated a clinical response at week 8) who subsequently enrolled into OCTAVE Sustain to receive placebo and experienced treatment failure, and subsequently enrolled into OCTAVE Open to receive tofacitinib 10 mg b.d. and achieved a clinical response at month 2 of OCTAVE Open.

[f]Induction responders who subsequently enrolled into OCTAVE Sustain to receive tofacitinib 5 mg b.d. and experienced treatment failure, and dose escalated to tofacitinib 10 mg b.d. in OCTAVE Open and achieved a clinical response at month 2 of OCTAVE Open; 2 patients (protocol deviations) were assigned to receive tofacitinib 5 mg b.d. and 33 patients were assigned to receive tofacitinib 10 mg b.d. in OCTAVE Open.

[g]Includes all the other reasons for withdrawal from the study.

[h]Considered treatment discontinuation events in the persistence analysis.

[i]RIVETING (NCT03281304) is an ongoing, randomised, parallel-group study designed to evaluate the efficacy and safety of tofacitinib in patients with UC who were in stable remission on tofacitinib 10 mg b.d.

[j]Discontinuation post-regulatory approval was mandatory as per regulatory requirements in Japan.

willingness to participate and adverse event (Table 3). Compared with responders, a numerically higher proportion of delayed responders, retreatment responders and dose escalation responders discontinued due to an insufficient clinical response.

A total of 116 (19.2%) patients discontinued OCTAVE Open to enrol into RIVETING. In Japan, 12 (2.0%) patients enrolled into post-marketing surveillance and 3 (0.5%) patients discontinued the study following regulatory approval. These events were censored in the Kaplan-Meier and Cox proportional hazards analyses of persistence.

## 4 | DISCUSSION

In this analysis, the persistence of tofacitinib treatment during long-term follow-up (up to 7 years) was evaluated using data from OCTAVE Open in patients with UC. Patients could enrol into OCTAVE Open having completed or demonstrated treatment failure during the 52-week maintenance study, or if they were non-responders after completing the 8-week induction studies. The different patient subpopulations reflect real-life scenarios encountered by patients presenting with UC in clinical practice. Of the patients eligible to enrol into OCTAVE Open, this analysis included patients who enrolled with a clinical response and those who, per protocol, were not required to withdraw due to a lack of clinical response at week 8 of OCTAVE Open. Among these patients who showed a benefit from tofacitinib treatment either at baseline of OCTAVE Open or after 8 weeks of treatment, a high proportion maintained treatment, with the median survival ranging from 4.0 years in retreatment responders to 5.6 years in all responders.

Using tofacitinib treatment persistence as a surrogate for efficacy, safety and tolerability, these results are consistent with previously reported data in the same subpopulations of patients in OCTAVE Open after a follow-up of up to 3 years.[10-13]

Although persistence was high across patient subpopulations in OCTAVE Open, some differences across patient subgroups were identified in the current analysis. Median drug survival was greatest among patients who had experienced a clinical response before enrolment into OCTAVE Open (5.6 years, with 2- and 5-year estimated drug survival of 73.9% and 54.5%, respectively) compared with patients who were classified as delayed responders, retreatment responders and dose escalation responders. For these groups, median drug survival was generally similar (4.5, 4.0 and 4.4 years, respectively). When analysed by remission status at entry into OCTAVE Open, tofacitinib treatment persistence was numerically higher among responders in remission with 2- and 5-year tofacitinib persistence rates of 76.8% and 56.9% compared with 69.8% and 50.0% among responders not in remission, respectively. These data are consistent with the previously reported durable efficacy of tofacitinib in patients who achieved remission in OCTAVE Sustain and maintained remission for up to 3 years in OCTAVE Open.[10]

In this study, 26.2% of responders in remission required an initial tofacitinib dose increase from 5 to 10 mg b.d. The recapture of remission in these patients has previously been reported and at 3 months post-dose increase, 75% of patients achieved partial Mayo score remission (defined as a partial Mayo score ≤2 with no individual subscore >1).[10]

Previous analyses evaluated the efficacy and safety of extended induction for an additional 8 weeks of tofacitinib treatment in patients who did not achieve a response following an initial 8-week induction. In these patients who received 16 weeks of induction treatment with tofacitinib 10 mg b.d., 70.3% and 56.1% of patients had a clinical response at month 12 and month 36 of OCTAVE Open, respectively.[11] Among the delayed responder subpopulation in this analysis, median drug survival was 4.5 years, with 2- and 5-year estimated drug persistence rates of 69.5% and 45.2%, respectively.

In OCTAVE Open, among the patients who were randomised to receive tofacitinib 5 mg b.d. during OCTAVE Sustain and experienced a loss of clinical response, 54.7% of patients had recaptured clinical response at month 24 following dose escalation back to tofacitinib 10 mg b.d.[12] In the analysis of persistence described here, the estimated time to discontinuation for dose escalation responders was 4.4 years, with 2- and 5-year estimated drug persistence rates of 74.3% and 32.8%, respectively.

It is also recognised that treatment interruption may occur in patients with UC for a diverse range of reasons. In patients with a prior response to tofacitinib 10 mg b.d. induction therapy who then experienced a loss of response whilst receiving placebo during OCTAVE Sustain, retreatment with tofacitinib 10 mg b.d. in OCTAVE Open was generally efficacious. Retreatment with tofacitinib was associated with clinical response in 74.0% and 48.5% of patients at month 2 and month 36, respectively.[13] Among retreatment responders, the estimated time to discontinuation was 4 years, with 2- and 5-year estimated drug persistence rates of 70.7% and 40.0%, respectively.

The tofacitinib treatment persistence observed in this analysis of patients in OCTAVE Open is similar to that seen in patients with rheumatoid arthritis (median drug persistence of 5 years),[14] but higher than the previously reported drug persistence rates for tofacitinib in patients with UC in a real-world setting.[15-18] In these studies, tofacitinib treatment persistence in patients with UC ranged from 53% to 71% at 6 months,[15-20] and from 51% to 58.8% at approximately 1 year.[16-18] In addition, data from a large healthcare database showed that the real-world persistence to tofacitinib in patients with UC was similar to biological therapy persistence (including TNFi and anti-integrin treatment; 44.8% after 1 year).[21] It is possible that patients outside of clinical trials represent a more treatment refractory UC patient population compared with patients who enrol into clinical trials.

Treatment discontinuation in patients with UC may occur for many reasons, including loss of efficacy or poor tolerability. Here, the most common reason for discontinuation across all subpopulations was insufficient clinical response, although the proportion of patients discontinuing for this reason was numerically higher among delayed responders, dose escalation responders and retreatment responders, compared with responders in remission and responders not in remission. From the Cox regression analysis,

patients who were younger (<40 years), female or assigned to receive tofacitinib 10 mg b.d. at OCTAVE Open baseline were more likely to discontinue tofacitinib treatment due to any reason and patients who were younger (<40 years), assigned to receive tofacitinib 10 mg b.d. at OCTAVE Open baseline or had prior TNFi failure were more likely to discontinue due to insufficient clinical response. Consistent with these findings, female gender and younger age (18–25 years) were identified as predictors of biological therapy discontinuation in a retrospective real-world study of patients with Crohn's disease and UC.[21] There are several outcomes indicative of a more severe disease course, including progression of disease extension and relapse rates, for which predictive factors have been identified.[22] The 5-year follow-up IBSEN study found that relapse was more frequent in young patients and more frequent in female patients.[23] Tofacitinib dose assignment upon entry to OCTAVE Open was based on remission status with patients not in remission assigned to tofacitinib 10 mg b.d. and, hence, could be a surrogate for more active disease.

Limitations of this analysis include the open-label design of the OCTAVE Open study, and the post hoc nature of the analyses, such that the studies were neither designed nor powered to detect potential differences in treatment persistence. In addition, the small number of patients in some subgroups may preclude drawing clinically meaningful interpretations. Furthermore, interpretation of these results should take into account that persistence reflects patients who continued treatment and remained in the trial over time, rather than providing direct evidence of disease activity.

In conclusion, high levels of tofacitinib treatment persistence was observed across the selected subpopulations of patients analysed in the OCTAVE Open open-label, long-term extension study that followed patients for up to 7 years, with median time to discontinuation ranging from 4.0 to 5.6 years. These data further support the use of tofacitinib in the long-term management of UC. Further research should focus on factors to enhance persistence with tofacitinib treatment in patients with UC.

## CONFLICT OF INTERESTS

RP has received advisory and/or consultation fees from AI4GI, AbbVie, Amgen, Arena Pharmaceuticals, Atlantic Healthcare, BioBalance, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coronado Biosciences, Cosmo Technologies, Eagle, Eisai Medical Research, Elan, Eli Lilly, EnGene, Ferring Pharmaceuticals, Genentech, Gilead Sciences, Given Imaging, GlaxoSmithKline, Innomar, Janssen, Lycera, Meda, Merck & Co., Merck Research Laboratories, Novo Nordisk, PDL Biopharma, Pfizer Inc, Prometheus Laboratories, Protagonist, Receptos, Robarts Clinical Trials, Sandoz, Sanofi Genzyme, Satisfai Health, Shire Pharmaceuticals, Sigmoid Pharma, Specialty Rx, Sublimity, Takeda and TherAdvance. MTA has served as a trainer/lecturer for Cornerstones Health, Inc, Focus Medical Communications, Imedex, Janssen and Prime CME; and has served as a consultant or advisor to AbbVie, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Gilead Sciences, Prometheus Biosciences, Takeda and UCB Biopharma SRL. IL is an employee of IQVIA, which was a paid contractor to Pfizer in connection with the development of this manuscript and in providing statistical support. RM, NL, LS and JCW are all employees and stockholders of Pfizer Inc. BES has received consulting fees from 4D Pharma, AbbVie, Allergan, Amgen, Arena Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Boston Pharmaceuticals, Capella Biosciences, Celgene, Celltrion Healthcare, Eli Lilly, EnGene, Ferring Pharmaceuticals, Genentech, Gilead Sciences, Hoffmann-La Roche, Immunic, Ironwood Pharmaceuticals, Janssen, Lyndra, MedImmune, Morphic Therapeutic, Oppilan Pharma, OSE Immunotherapeutics, Otsuka, Palatin Technologies, Pfizer Inc, Progenity, Prometheus Laboratories, Redhill Biopharma, Rheos Medicines, Seres Therapeutics, Shire Pharmaceuticals, Synergy Pharmaceuticals, Takeda, Target RWE, Theravance Biopharma R&D, TiGenix and Vivelix Pharmaceuticals; has received honoraria for speaking in CME programmes from Eli Lilly, Genetech, Gilead Sciences, Janssen, Pfizer Inc and Takeda; and has received research funding from Celgene, Janssen, Pfizer Inc, Takeda and Theravance Biopharma R&D. MC has served as a speaker, consultant and advisory member for, or received research funding from, AbbVie, Celltrion, Chiesi, Faes Farma, Falk Pharma, Ferring Pharmaceuticals, Gebro Pharma, Janssen, MSD, Otsuka Pharmaceuticals, Pfizer Inc, Roche, Shire Pharmaceuticals, Takeda and Tillotts Pharma.

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## AUTHORS' CONTRIBUTIONS

NL planned and conducted the studies. NL, RM, JCW, IL and LS planned the analysis. RP, MTA, IL, RM, NL, LS, JCW, BES and MC collected or interpreted data. All authors drafted and edited the manuscript, and approved the final version of the article, including the authorship list.

## DATA AVAILABILITY STATEMENT

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

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## SUPPORTING INFORMATION

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

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