Health-Related Quality of Life Outcomes With Tofacitinib Treatment in Patients With Ulcerative Colitis in the Open-Label Extension Study, OCTAVE Open

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Background: Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of ulcerative colitis. We report health-related quality of life (HRQoL) outcomes in patients with ulcerative colitis in the phase 3 open-label, long-term extension study, OCTAVE Open.

Methods: The Inflammatory Bowel Disease Questionnaire (IBDQ), EuroQoL-5 Dimensions Health Questionnaire, and 36-Item Short Form Survey scores were analyzed up to month (M) 72 in 4 subpopulations: patients in remission at baseline (maintenance remitters) assigned tofacitinib 5 mg twice daily and patients not in remission at baseline (maintenance nonremitters, maintenance treatment failures, and induction nonresponders [IndNRs]) assigned tofacitinib 10 mg twice daily in OCTAVE Open. Data were analyzed overall and stratified by corticosteroid use at baseline, prior tumor necrosis factor inhibitor failure, and prior immunosuppressant failure.

Results: Among maintenance remitters and nonremitters, HRQoL outcomes were maintained up to M72: 80.0% and 100.0% of patients had an IBDQ total score ≥170, respectively. At baseline, 74% of maintenance treatment failures had an IBDQ total score ≥170, and this increased to 54.3% and 75.0% at M2 and M72, respectively. Corresponding values for IndNRs were 22.6%, 51.0%, and 86.0%. HRQoL outcomes were independent of treatment history. Among patients not in remission at baseline, improvement in EuroQoL-5 Dimensions Health Questionnaire and 36-Item Short Form Survey scores was maintained or achieved by M2, and steady to M72 or M33, with maintenance treatment failures and IndNR subpopulations undergoing the biggest improvements from baseline.

Conclusions: A continued favorable impact on HRQoL was revealed with long-term tofacitinib treatment in OCTAVE Open, regardless of baseline remission status or treatment history. (ClinicalTrials.gov; number: NCT01470612).

Lay Summary
Health-related quality of life was assessed in patients with ulcerative colitis in an open-label, long-term extension study, OCTAVE Open. Patients had sustained beneficial effects on health-related quality of life with long-term tofacitinib treatment, regardless of treatment history/remission status at OCTAVE Open baseline.

Key Words: tofacitinib, ulcerative colitis, quality of life

INTRODUCTION
Ulcerative colitis (UC) is a long-term condition that affects the large intestine, identified by inflammation in periods of flare, with intermittent periods of latency.1 Patients often present with bloody stools, with other symptoms including increased frequency of bowel movements, urgency, incontinence, mucus discharge, fatigue, and nighttime bowel movements,2 and these physical manifestations directly affect patients’ health-related quality of life (HRQoL). These physical symptoms can also have a detrimental effect on patients’ emotional well-being; patients with inflammatory bowel disease (IBD), inclusive of UC, report higher anxiety and depression levels than the general population.3,4 A recent global survey reported that most patients felt that UC controlled their lives and that they found the condition mentally exhausting.2 Psychological symptoms are commonly reported in patients with IBD and can adversely affect HRQoL. Anxiety and depression levels have been found...
to be greater in those with active vs inactive IBD. As such, treatments for UC that enhance clinical outcomes may also result in improved HRQoL.

Formal instruments have been developed to assess HRQoL in patients with IBD, the most widely used and validated being the Inflammatory Bowel Disease Questionnaire (IBDQ). Other generic instruments include, but are not limited to, EuroQoL-5 Dimensions Health Questionnaire (EQ-5D) and 36-Item Short Form Survey (SF-36). Each of these surveys covers different domains, including physical symptoms, social functioning, and general health. Improvement in HRQoL is increasingly becoming a major target of UC treatment, alongside traditional clinical and endoscopic goals.

Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of UC. The efficacy and safety of tofacitinib have been evaluated in three phase 3, randomized, placebo-controlled studies (OCTAVE Induction 1 and 2 and OCTAVE Sustain) and in an open-label, long-term extension study (OCTAVE Open) in patients with moderately to severely active UC. Previous analyses of the tofacitinib phase 3 studies have shown significant improvements in HRQoL with up to 52 weeks of tofacitinib therapy vs placebo.

These post hoc analyses from OCTAVE Open evaluate the effect of long-term (up to month 72) tofacitinib treatment on patients’ HRQoL using the IBDQ tailored to IBD and the general EQ-5D and SF-36 (up to month 33). Patients were analyzed by remission status at the start of OCTAVE Open, and further split by corticosteroid use at induction study baseline, prior tumor necrosis factor (TNF) inhibitor failure, and prior immunosuppressant failure.

METHODS

Patients and Study Design

OCTAVE Open (NCT01470612) was a phase 3 study in which patients received tofacitinib 5 or 10 mg twice daily (BID) for up to 7.0 years. Patients could enter OCTAVE Open from the induction and maintenance studies, OCTAVE Induction 1 and 2 (NCT01465763 and NCT01458951), and OCTAVE Sustain (NCT01458574), respectively. Full study design details have been reported previously. Briefly, OCTAVE Induction 1 and 2 were two identical, 8-week, phase 3 induction studies where patients with moderately to severely active UC were randomized to receive either tofacitinib 10 mg BID or placebo. Patients with clinical response at the end of OCTAVE Induction 1 and 2 were eligible to enroll in OCTAVE Sustain, a 52-week maintenance study, and were randomized to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, or placebo.

Patients were eligible to enroll in OCTAVE Open if they were nonresponders after completing OCTAVE Induction 1 or 2, or had completed or withdrawn early (after experiencing treatment failure) from OCTAVE Sustain.

Analyses are presented for 4 subpopulations of patients who enrolled in OCTAVE Open (Figure 1). Patients who

Figure 1. Overview of the tofacitinib treatment sequences for patients in the maintenance remitter, maintenance nonremitter, maintenance treatment failure, and induction nonresponder (IndNR) subpopulations. 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 ≥8 weeks of maintenance therapy. Final complete efficacy assessment at week 8 or 52. Treatment continued up to week 9 or 53. BID, twice daily; N, number of patients in each subpopulation.

Key Messages:

• What is already known? In patients with ulcerative colitis (UC), tofacitinib induction and maintenance therapy have been shown to significantly improve health-related quality of life (HRQoL) up to 52 weeks, compared with placebo.

• What is new here? Long-term (up to 6 years) maintenance therapy with tofacitinib 5 or 10 mg twice daily can sustain beneficial effects on HRQoL, regardless of prior remission or responder status, or treatment history.

• How can this study help patient care? These findings provide insights around the effect of tofacitinib on HRQoL in different UC patient populations and clinical scenarios, including in the context of dosing.
completed OCTAVE Sustain and were in remission (maintenance remitters) were assigned to receive tofacitinib 5 mg BID, and patients who completed OCTAVE Sustain and were not in remission (maintenance nonremitters) were assigned to receive tofacitinib 10 mg BID. Patients with treatment failure between baseline (week 8 of OCTAVE Induction 1 and 2) and week 52 of OCTAVE Sustain (maintenance treatment failures) could enter OCTAVE Open and receive tofacitinib 10 mg BID. Patients without clinical response at the end of OCTAVE Induction 1 and 2 (tofacitinib induction nonresponders [IndNRs]) could enter OCTAVE Open, in which they were assigned tofacitinib 10 mg BID. IndNRs without a clinical response after an additional 8 weeks (total of 16 weeks tofacitinib 10 mg BID induction therapy) were required to discontinue.

Oral corticosteroids (prednisone equivalent up to 25 mg/d; budesonide up to 9 mg/d) were allowed during OCTAVE Induction 1 and 2, as long as the dose was steady for at least 2 weeks before baseline of OCTAVE Induction 1 and 2 and during those studies. Corticosteroid tapering was mandatory at the beginning of OCTAVE Sustain. Patients receiving corticosteroids who entered OCTAVE Open were also required to taper their corticosteroid dose, from the first week of the study, to achieve steroid-free status. The daily dose of oral prednisone or equivalent was reduced by 5 mg/wk until the dose reached 20 mg/d, then reduced by 2.5 mg/wk to 5.0 mg/wk until the dose reached 0 mg/d. However, patients could continue in the study with a corticosteroid dose of no more than 10 mg/d (prednisone or equivalent) if they were unable to endure tapering. Concomitant treatment with azathioprine, 6-mercaptopurine, methotrexate, or TNF inhibitor was prohibited in OCTAVE Open.

**HRQoL Outcomes**

**Inflammatory Bowel Disease Questionnaire**
The IBDQ is a psychometrically validated instrument for measuring IBD-specific quality of life. The IBDQ includes 32 items stratified by 4 domains: bowel symptoms (total domain score range, 10-70), systemic symptoms (total domain score range, 5-35), emotional function (total domain score range, 12-84), and social function (total domain score range, 5-35). For the total score (range, 32-224) and each domain, a greater score implies an improved quality of life. A score ≥170 corresponds to clinical remission, and a ≥16-point increase is accepted as an indication of an important improvement clinically. In OCTAVE Open, patients measured their own IBDQ at the start of OCTAVE Open and at months 2, 6, 12, 18, 24, 30, 36, 48, 60, and 72.

**EuroQol-5 Dimensions Health Questionnaire**
The EQ-5D is a tool to assess overall health used across several disease areas that allows patients to define their health according to 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. One single utility index is determined from the scores of all 5 domains, with 0 representing death and 1 representing perfect health. In addition, an EQ-5D also consists of an independent visual analog scale (VAS) that varies from 0 (worst imaginable health state) to 100 (best imaginable health state). In OCTAVE Open, the EQ-5D was self-administered by patients monthly from baseline to month 4, at month 6, once a quarter until month 36, and at months 48, 60, and 72.

### Statistical Analysis
Baseline demographics and clinical characteristics were summarized descriptively. The full analysis set included all subjects who received at least 1 dose of tofacitinib 5 or 10 mg BID in OCTAVE Open.

For HRQoL outcomes, both observed and nonresponder imputation (NRI) last observation carried forward (LOCF) data are reported. NRI was applied for missing data at all visits, and LOCF was applied after a patient advanced to a subsequent study up to the visit they would have reached if they had stayed in the study.

The proportion of patients with IBDQ total score ≥170 was a binary efficacy endpoint in OCTAVE Open, reported at baseline and at months 2, 12, 24, 36, and 72, and analyzed overall and further stratified by corticosteroid use at baseline of induction studies, prior TNF inhibitor failure, and prior immunosuppressant failure. Proportions of patients stratified by treatment history (corticosteroid use at the start of OCTAVE Induction 1 and 2, prior TNF inhibitor failure, and prior immunosuppressant failure) with IBDQ total score ≥170 could not be assessed beyond month 60 because of small patient numbers in some subpopulations. Exploratory IBDQ endpoints included the proportion of patients with a ≥16-point increase from the start of OCTAVE Induction 1 and 2 and change from baseline at OCTAVE Open over time in IBDQ total score, up to month 72. Exploratory endpoints also included change from baseline at OCTAVE Open in EQ-5D utility index score and EQ-5D VAS score over time, reported at baseline and at months 2, 12, 24, 36, and 72, and change from baseline at OCTAVE Open in SF-36 physical functioning domain, social functioning domain, and vitality domain over time, reported at baseline and at months 1, 9, 21, and 33.

### Ethical Considerations
All trials were conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines and approved by the Institutional Review Board and/or Independent Ethics Committee at each investigational center participating in the studies or at a central Institutional Review Board. All patients provided written informed consent.

### RESULTS

#### Patients
Baseline demographics and clinical characteristics for each of the subpopulations are shown in Table 1.
Baseline demographics were broadly comparable between subpopulations. Among the maintenance remitters (n = 163), less patients had prior TNF inhibitor failure (38.7%) compared with patients not in remission at baseline of OCTAVE Open: maintenance nonremitters (n = 109 [45.0%]), maintenance treatment failures (n = 216 [46.8%]), and IndNRs (n = 429 [60.8%]). A similar trend was observed for prior immunosuppressant failure (62.0% vs 78.0%, 75.5%, and 77.2%, respectively). Corticosteroid use at the start of induction studies was similar between maintenance remitters, maintenance nonremitters, and IndNR subpopulations (39.3%, 37.6%, and 42.0%, respectively) and was higher in the maintenance treatment failure subpopulation (58.8%). Corticosteroid use at baseline of OCTAVE Open was low to absent in the maintenance remitter (0.6%), maintenance treatment failure (11.6%), and maintenance nonremitter (0.0%) subpopulations, and it was highest in the IndNR subpopulation (41.7%).

HRQoL Outcomes: IBDQ

**IBDQ Outcomes in Patients in Remission at OCTAVE Open Baseline**

Among the maintenance remitters who entered OCTAVE Open in remission and were assigned to receive tofacitinib 5 mg BID treatment, the mean IBDQ total score at baseline was 200.3 ± 16.8 (Table 1); 94.5% of patients had an IBDQ total score ≥170 at baseline of OCTAVE Open (observed) (Figure 2A). At months 36 and 72 of OCTAVE Open, 88.0% and 80.0% of patients, respectively, had an IBDQ total score ≥170 (observed) (Figure 2A). The proportion of patients with a ≥16-point increase in IBDQ total score from induction baseline was also generally maintained up to month 72 in this population (Figure 2B); the mean IBDQ total score at induction baseline was 121.7 ± 32.1 (observed) among all tofacitinib 10 mg BID-treated patients (n = 900) and 121.4 ± 31.2 (observed) among all placebo-treated patients (n = 234). Furthermore, the difference from baseline at OCTAVE Open in IBDQ total score over time was minimal among maintenance remitters (-3.6 ± 17.1, -1.8 ± 18.8, and -5.4 ± 38.9 at months 2, 36, and 72, respectively) (observed) (Figure 2C); Corresponding NRI-LOCF data are shown in Supplementary Figure 1. The changes from baseline at OCTAVE Open in the 4 individual IBDQ domains followed similar trends to the differences from baseline in the IBDQ total score (Supplementary Figure 2).

Within each subpopulation, the proportions of patients with IBDQ total score ≥170 up to month 60 were similar regardless of prior treatment history (Figure 3A-3C) (observed data). Corresponding NRI-LOCF data are shown in Supplementary Figure 3.

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### Table 1. Baseline Demographics and Clinical Characteristics of Patients Who Entered OCTAVE Open in Remission or Not in Remission (FAS, Observed)

<table>
<thead>
<tr>
<th></th>
<th>Maintenance Remitters (n = 163)</th>
<th>Maintenance Nonremitters (n = 109)</th>
<th>Maintenance Treatment Failures (n = 216)</th>
<th>IndNRs (n = 429)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib dose in OCTAVE Open, mg BID</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>44.8 ± 14.7</td>
<td>43.2 ± 12.9</td>
<td>41.6 ± 13.3</td>
<td>39.5 ± 13.6</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>75 (46.0)</td>
<td>41 (37.6)</td>
<td>95 (44.0)</td>
<td>168 (39.2)</td>
</tr>
<tr>
<td>Disease duration, y, mean ± SDa</td>
<td>7.7 ± 6.6</td>
<td>9.3 ± 7.8</td>
<td>8.2 ± 7.4</td>
<td>7.6 ± 6.5</td>
</tr>
<tr>
<td>Disease extent, n (%)b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctosigmoiditis</td>
<td>34 (21.0)</td>
<td>12 (11.1)</td>
<td>24 (11.2)</td>
<td>64 (14.9)</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>53 (32.7)</td>
<td>29 (26.9)</td>
<td>75 (34.9)</td>
<td>150 (35.0)</td>
</tr>
<tr>
<td>Extensive colitis/pancolitis</td>
<td>75 (46.3)</td>
<td>67 (62.0)</td>
<td>115 (53.5)</td>
<td>215 (50.1)</td>
</tr>
<tr>
<td>Prior TNF inhibitor failure, n (%)b</td>
<td>63 (38.7)</td>
<td>49 (45.0)</td>
<td>101 (46.8)</td>
<td>261 (60.8)</td>
</tr>
<tr>
<td>Prior immunosuppressant failure, n (%)b</td>
<td>101 (62.0)</td>
<td>85 (78.0)</td>
<td>163 (75.5)</td>
<td>331 (77.2)</td>
</tr>
<tr>
<td>Baseline corticosteroid use, n (%)b</td>
<td>64 (39.3)</td>
<td>41 (37.6)</td>
<td>127 (58.8)</td>
<td>180 (42.0)</td>
</tr>
<tr>
<td>Endoscopic improvement, n (%)aef</td>
<td>163 (100.0)</td>
<td>19 (17.4)</td>
<td>1 (0.5)g</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Clinical response, n (%)aef</td>
<td>163 (100.0)</td>
<td>92 (84.4)</td>
<td>9 (4.2)g</td>
<td>0 (0.0)h</td>
</tr>
<tr>
<td>Remission, n (%)aef</td>
<td>163 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)g</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PMS, mean ± SDa</td>
<td>0.4 ± 0.5</td>
<td>2.0 ± 1.7</td>
<td>6.6 ± 1.5</td>
<td>5.8 ± 1.4</td>
</tr>
<tr>
<td>Total Mayo score, mean ± SDa</td>
<td>1.0 ± 0.7</td>
<td>4.0 ± 1.8</td>
<td>9.2 ± 1.6</td>
<td>8.6 ± 1.6</td>
</tr>
<tr>
<td>IBDQ total score, mean ± SDa</td>
<td>200.3 ± 16.8</td>
<td>186.8 ± 27.4</td>
<td>117.6 ± 34.4</td>
<td>138.2 ± 36.5</td>
</tr>
</tbody>
</table>

Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. Abbreviations: BID, twice daily; FAS, full analysis set; IBDQ, Inflammatory Bowel Disease Questionnaire; IndNR, induction nonresponder; PMS, partial Mayo score; TNF, tumor necrosis factor.

1Baseline of OCTAVE Open.
2Baseline of OCTAVE Open.
3Baseline of induction studies.
4Maintenance remitters (n = 162), maintenance nonremitters (n = 108), maintenance treatment failures (n = 215).
5Maintenance treatment failure subpopulation: 1 patient with proctitis was enrolled as a protocol deviation.
6Endoscopic improvement (defined as mucosal healing in the OCTAVE Open protocol [NCT01470612]) was defined as a Mayo endoscopic subscore of 0 or 1.
7Based on centrally read endoscopic subscore.
8n = 215.
9n = 427.
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Among the subpopulations of patients not in remission at OCTAVE Open baseline and were assigned to receive tofacitinib 10 mg BID treatment, mean IBDQ total score at baseline of OCTAVE Open was higher among maintenance nonremitters compared with maintenance treatment failures and IndNRs (186.8 ± 27.4 vs 117.6 ± 34.4 and 138.2 [36.5, respectively) (Table 1).

Among the maintenance nonremitters, 77.1% of patients had an IBDQ total score ≥170 at baseline of OCTAVE Open (observed) (Figure 2A). At months 36 and 72 of OCTAVE Open, 87.0% and 100.0% of patients, respectively, had an IBDQ total score ≥170 (observed) (Figure 2A). The proportion of maintenance nonremitters with a ≥16-point increase in IBDQ total score from induction baseline was maintained up to month 72 (Figure 2B).

Furthermore, the change from baseline at OCTAVE Open in IBDQ total score at months 2, 36, and 72 was minimal: 5.1 ± 23.9, 11.4 ± 23.0, and 6.0 ± 12.4, respectively (Figure 2C). Corresponding NRI-LOCF data are shown in Supplementary Figure 1.

In contrast, the proportions of patients with an IBDQ total score ≥170 at baseline of OCTAVE Open were lower among maintenance treatment failures (7.4%) and IndNRs (22.6%). However, these subpopulations experienced the largest improvements in IBDQ outcomes over time in OCTAVE Open. The proportions of maintenance treatment failures with an IBDQ total score ≥170 were 54.3%, 83.2%, and 75.0% at months 2, 36, and 72, respectively (observed) (Figure 2A). Corresponding values for IndNRs were 51.0%, 87.1%, and 86.0%. A comparable trend was revealed among the proportion of patients with a ≥16-point increase in IBDQ total score from induction baseline up to month 72 in the maintenance treatment failure and IndNR subpopulations (observed) (Figure 2B).

Likewise, the difference from baseline to month 2 in IBDQ total score was higher among maintenance treatment failures and IndNRs compared with maintenance nonremitters. Among the maintenance treatment failure subpopulation, the

**IBDQ Outcomes in Patients Not in Remission at OCTAVE Open Baseline**

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Likewise, the difference from baseline to month 2 in IBDQ total score was higher among maintenance treatment failures and IndNRs compared with maintenance nonremitters. Among the maintenance treatment failure subpopulation, the
changes from baseline in IBDQ total score at months 2, 36, and 72 were 48.6 ± 42.3, 73.4 ± 35.8, and 63.6 ± 43.5, respectively (observed) (Figure 2C). Corresponding values for the IndNR subpopulation were 23.5 ± 35.1, 51.2 ± 35.0, and 48.8 ± 28.3. Corresponding NRI-LOCF data are shown in Supplementary Figure 1. Similar to the maintenance remitter subpopulation, the changes from baseline at OCTAVE Open in the 4 individual IBDQ domains followed similar trends to the changes from baseline in IBDQ total score (Supplementary Figure 3).

Among maintenance nonremitters, the mean EQ-5D utility index score and EQ-5D VAS score at baseline of OCTAVE Open were 0.90 ± 0.15 and 82.27 ± 13.34, respectively. Corresponding scores were 0.61 ± 0.27 and 45.45 ± 20.14 in the maintenance treatment failures and 0.71 ± 0.24 and 55.65 ± 19.97 in IndNRs.

Among the maintenance nonremitters, the EQ-5D utility index score and EQ-5D VAS score were maintained up to month 72 with minimal differences from baseline. The mean changes from baseline in EQ-5D utility index score and EQ-5D VAS score at month 72 were 0.05 ± 0.10 and 4.25 ± 9.88, respectively (Figure 4A and 4B). In contrast, the mean changes from baseline to month 2 in the EQ-5D utility index score and EQ-5D VAS score were higher among the maintenance treatment failure and IndNR subpopulations, and the trend for higher mean change from baseline was maintained up to month 72. Among the maintenance treatment failures, differences from baseline in EQ-5D utility index score at months 2 and 72 were 0.20 ± 0.30 and 0.28 ± 0.31, respectively (Figure 4A). The changes from baseline in EQ-5D VAS score at months 2 and 72 were 25.78 ± 22.79 and 20.25 ± 28.80, respectively (Figure 4B). Corresponding values for the IndNR subpopulation at months 2 and 72 were 0.09 ± 0.23 and 0.17 ± 0.18 (EQ-5D utility index score) and 11.51 ± 17.32 and 23.65 ± 16.74 (EQ-5D VAS score) (Figures 4A and 4B). Similar trends were observed in SF-36 physical, social functioning, and vitality domain scores in all subpopulations up to month 33 (Figure 5). Corresponding NRI-LOCF data are shown in Supplementary Figure 4 (EQ-5D) and Supplementary Figure 5 (SF-36).

Overall, the change in HRQoL outcomes over time align with the temporal change in clinical endpoints observed in OCTAVE Open (Supplementary Figure 6).

DISCUSSION

This post hoc analysis aimed to investigate tofacitinib's long-term effect on HRQoL outcomes in OCTAVE Open up to month 72, adding to the previous study that demonstrated improved HRQoL with tofacitinib therapy in the induction and maintenance studies. This analysis evaluated the effect...
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of remission status at OCTAVE Open baseline and subsequent dose received in OCTAVE Open on HRQoL outcomes, as well as the effect of treatment history. Continued benefits to HRQoL were ascertained in patients receiving long-term tofacitinib treatment in OCTAVE Open. In maintenance remitters, who entered OCTAVE Open in remission, improvements in all HRQoL outcomes that were assessed during OCTAVE Induction 1 and 2 and OCTAVE Sustain were maintained long-term with tofacitinib therapy. In patients who entered OCTAVE Open not in remission and

Figure 4. Mean change from baseline in (A) EuroQoL-5 Dimensions Health Questionnaire (EQ-5D) utility index score and (B) EQ-5D visual analog scale (VAS) score in OCTAVE Open (full analysis set, observed). Scores from the 5 domains are used to calculate a single utility index score anchored at 0 for death and 1 for perfect health. In addition, an EQ-5D also includes a separate visual analog scale (EQ-5D VAS) that varies from 0 (worst imaginable health state) to 100 (best imaginable health state). BID, twice daily; IndNRs, induction nonresponders; N, number of patients with non-missing values.

Figure 5. Mean change from baseline in (A) 36-Item Short Form Survey (SF-36) physical functioning score, (B) SF-36 social functioning score, and (C) SF-36 vitality score in OCTAVE Open (full analysis set, observed). SF-36 components are scored from 0 (worst health) to 100 (best health). BID, twice daily; IndNRs, induction nonresponders; N, number of patients with non-missing values.
received tofacitinib 10 mg BID, HRQoL improvements were observed within the first 8 weeks, and were sustained up to month 72, regardless of prior treatment history.

Assessment of HRQoL in patients with UC is becoming increasingly important, with the STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) guidelines recommending that restoration of HRQoL should be a long-term goal of UC treatment. Furthermore, draft guidance from the U.S. Food and Drug Administration advises that the efficacy of new UC therapies in clinical trials should be assessed using patient-reported outcomes as well as endoscopic and histologic evaluation.

IBDQ is an IBD-specific instrument to check HRQoL among patients with IBD, while the EQ-5D and SF-36 are universal self-reported measures of patients’ physical functioning and well-being. Previous analyses demonstrated that tofacitinib 10 mg BID induction therapy significantly improved IBDQ score vs placebo at week 8, and improvements were maintained through 52 weeks of maintenance therapy with tofacitinib 5 and 10 mg BID. Furthermore, the same trend was observed when differences from baseline in SF-36 scores were assessed.

Significant but not strong correlations have been described between IBDQ total scores and Mayo scores between the end of OCTAVE Induction and OCTAVE Sustain in previous studies. The correlation between HRQoL and clinical outcomes could not be adequately addressed in OCTAVE Open as endoscopy was only performed yearly up to month 36; however, the change from baseline in the proportion of patients with partial Mayo score ≤2 with no individual subscore >1 reflects the evolution of HRQoL. Moreover, the improvements in HRQoL observed in OCTAVE Open are in line with previous efficacy analyses that demonstrated improvements in clinical and endoscopic outcomes associated with tofacitinib-treated patients in OCTAVE Open. Data from the induction studies evaluated tofacitinib's effect on each IBDQ domain, and an improvement was evident in all items with tofacitinib induction therapy compared with placebo in patients with UC, with the greatest benefits reported in bowel symptoms domain items. The continued benefits to HRQoL recognized among patients on long-term tofacitinib treatment in OCTAVE Open aligned with the HRQoL outcomes reported in a study of the impact of other biologic therapies on HRQoL in patients with UC. Of these patients treated with vedolizumab during the GEMINI 1 study, the analysis determined that at week 6, 37% (n = 83 of 225) had an improvement in IBDQ score of ≥16 points from baseline (last observation carried forward), with 64% (n = 157 of 247) having the same point improvement from baseline to week 52. Moreover, the GEMINI 1 long-term safety study in patients with IBD treated with vedolizumab found a mean IBDQ total score of ≥160 was maintained from weeks 50 to 400 in patients with UC; HRQoL was comparable between patients regardless of TNF inhibitor failure history. In the ACT (Active Ulcerative Colitis Trial) 1 and 2 extension studies, patients with UC maintained improved HRQoL for up to 3 additional years with infliximab therapy; in year 3, the mean IBDQ total scores among patients treated with infliximab ranged from 182.6 to 191.2. However, it is of note that a post hoc analysis of data from OCTAVE Open showed that deterioration from baseline in IBDQ and SF-36 scores was noted in tofacitinib 5 mg BID-treated patients if they had extraintestinal manifestations at baseline.

In maintenance remitters who entered OCTAVE Open in remission and received tofacitinib 5 mg BID, HRQoL remission was maintained up to month 72 with tofacitinib therapy, regardless of prior treatment history. The high proportion of patients already with IBDQ total score ≥170 at baseline of OCTAVE Open supports the suggestion that improvement of clinical outcomes with UC therapy results in improved HRQoL. Long-term maintenance of HRQoL outcomes supports a previous post hoc analysis that reported that clinical efficacy outcomes, were maintained over time in the maintenance remitter subpopulation, with 68.3% (n = 97 of 142) and 50.4% (n = 71 of 141) of patients in remission at months 12 and 36 of OCTAVE Open, respectively (NRI-LOCF). The maintenance treatment failure and IndNR subpopulations experienced the largest improvements from baseline HRQoL outcomes. Patients in the maintenance treatment failure subpopulation entered OCTAVE Open after experiencing treatment failure in OCTAVE Sustain, while patients in the IndNR subpopulation entered OCTAVE Open directly after failing to achieve clinical response following 8 weeks of induction therapy with tofacitinib 10 mg BID; therefore, these subpopulations had a lower baseline HRQoL than the maintenance remitter or maintenance nonremitter subpopulations. Previous analyses have demonstrated that long-term clinical efficacy is achieved and maintained among patients who experienced treatment failure during OCTAVE Sustain and patients with delayed response to tofacitinib induction therapy who were assigned to receive tofacitinib 10 mg BID in OCTAVE Open. Among patients who experienced treatment failure during OCTAVE Sustain while receiving tofacitinib 5 mg BID and were subsequently assigned to receive tofacitinib 10 mg BID in OCTAVE Open, 57.9% (n = 33 of 57) and 64.9% (n = 37 of 57) of patients recaptured clinical response, and 35.1% (n = 20 of 57) and 49.1% (n = 28 of 57) were in remission, at months 2 and 12, respectively (NRI). Similarly, among patients who initially failed to respond to the initial 8 weeks of induction therapy with tofacitinib 10 mg BID, achieving clinical response only after an additional 8 weeks of induction therapy (16 weeks in total), 70.3% (n = 104 of 148) and 56.1% (n = 83 of 148) of patients had a clinical response at months 12 and 36 of OCTAVE Open, respectively. Therefore, delayed response or recapture of response following treatment failure, as demonstrated through clinical outcomes, may be reflected in improvements in HRQoL outcomes.

The maintenance nonremitter subpopulation showed the lowest improvement in HRQoL from baseline compared with the other subpopulations of patients not in remission at OCTAVE Open baseline; however, like the maintenance remitters, these patients had a higher baseline HRQoL, which was maintained up to month 72. The majority of maintenance nonremitters (84.4% [n = 92 of 109]) had clinical response at baseline of OCTAVE Open, suggesting that response, even in the absence of remission, is sufficient for achievement or maintenance of HRQoL outcomes. Overall, these data provide insights around different patient populations and clinical scenarios, including in the context of dosing.
as many patients will receive tofacitinib as second-line treatment, following primary or secondary loss of response to TNF inhibitor treatment.\textsuperscript{33} The observation that HRQoL outcomes improve irrespective of TNF inhibitor failure aligns with the findings for clinical endpoints in OCTAVE Induction 1 and 2: the treatment effect was similar between TNF inhibitor–experienced and –naïve patients.\textsuperscript{11}

The limitations of these analyses include that they are post hoc and that the self-reported nature of the HRQoL outcomes could be affected by reference bias. Moreover, these data were from OCTAVE Open, which has inherent limitations, including the absence of data from patients treated with placebo for comparison. The low patient numbers at the later time points when reporting IBDQ and SF-36 are a further limitation; this was in part due to patients entering additional studies; 140 patients discontinued to enroll in the phase 3b/4 RIVETING study, and a further 12 patients discontinued to enroll in a postmarketing surveillance study.\textsuperscript{12,26} It should be noted that the IndNR subpopulation entered OCTAVE Open directly from OCTAVE Induction 1 and 2; therefore, corticosteroid use was different compared with the other subpopulations who entered OCTAVE Open from OCTAVE Sustain, in which tapering of corticosteroids was mandatory.

CONCLUSIONS

Continued benefits to HRQoL were recognized among patients on long-term tofacitinib treatment in OCTAVE Open. In the maintenance remitter subpopulation, improvements in all HRQoL outcomes were sustained with tofacitinib 5 mg BID therapy. In patients who entered OCTAVE Open not in remission and received tofacitinib 10 mg BID, HRQoL improvements were noticed within the first 8 weeks, and were sustained up to month 72, regardless of treatment history including prior TNF inhibitor failure.

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Author Contribution

L.B., M.C.D., S.V., M.E., S.G., P.H., R.M., J.P., and D.T.R. made substantial contributions to the interpretation of the data. M.E., S.G., P.H., and R.M. contributed to the study design. RM contributed to the statistical analysis. All authors contributed to the development of the manuscript and critically reviewed/revised the manuscript for important intellectual content. All authors approved the final version of the manuscript before submission.

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Conflicts of Interest

L.B. has received consulting fees from AbbVie, Calypso, Esocap, Ewopharma, Dr. Falk Pharma, Ferring Pharmaceuticals, Janssen Pharmaceuticals, MSD, Pfizer Inc, Sanofi, Shire, Takeda, and Vifor. M.C.D. has received consulting fees from AbbVie, Arena, Bristol-Myers Squibb, Celgene, Eli Lilly, Galapagos, Gilead Sciences, Janssen Pharmaceuticals, Pfizer Inc, Prometheus Labs, Takeda, and UCB; and is a shareholder of Trellus Health. S.V. has received grant support from AbbVie, Galapagos, MSD, Pfizer Inc, and Takeda; speaker fees from AbbVie, Dr. Falk Pharma, Ferring Pharmaceuticals, Hospira, MSD, Takeda, and Tillotts; and consulting fees from AbbVie, AbolerIS Pharma, Alimentiv, Arena, AstraZeneca, Avaxia, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, CVasThera, Dr. Falk Pharma, Eli Lilly, Ferring Pharmaceuticals, Galapagos, Genentech/Roche, Gilead Sciences, Hospira, Imidomics, Janssen Pharmaceuticals, Johnson and Johnson, Materia Prima, MiroBio, Morphic, MrMHealth, MSD, Mundipharma, Pfizer Inc, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance Biopharma, Tillots Pharma AG, and Zealand Pharma. M.E., S.G., P.H., and R.M. are employees and stockholders of Pfizer Inc. J.P. has received personal fees from AbbVie, Arena, Athos, Boehringer Ingelheim, Celgene, Celltrion, Ferring Pharmaceuticals, Galapagos, Genentech/Roche, GlaxoSmithKline, Immunic, Janssen Pharmaceuticals, Mirum, Morphic, Nestlé, Origo, Pandion, Pfizer Inc, Progenity, Revolo, Takeda, Theravance Biopharma, and Wassermann; and received grant support from AbbVie and Pfizer Inc. D.T.R. has received consulting fees from AbbVie, Altrubio, Arena Pharmaceuticals, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corp/Syneos, Connect BioPharma, GalenPharma/Atlantica, Genentech/Roche, Gilead Sciences, InDex Pharmaceuticals, Iterative Scopes, Janssen Pharmaceuticals, Eli Lilly, Pfizer Inc, Prometheus Biosciences, Reistone, Takeda, and Techlab Inc; and received a research grant from Takeda.

DATA AVAILABILITY

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.

REFERENCES


