The Patient - Patient-Centered Outcomes Research (2023) 16:95–103
https://doi.org/10.1007/s40271-022-00603-w

ORIGINAL RESEARCH ARTICLE

Long-Term Improvement in the Patient-Reported Outcomes of Rectal Bleeding, Stool Frequency, and Health-Related Quality of Life with Tofacitinib in the Ulcerative Colitis OCTAVE Clinical Program

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Accepted: 20 September 2022 / Published online: 7 November 2022

Abstract

Background Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). The tofacitinib OCTAVE clinical program included phase III induction (OCTAVE Induction 1 and 2) and maintenance (OCTAVE Sustain) studies, and an open-label, long-term extension study (OCTAVE Open).

Objective This post hoc analysis assessed selected long-term, disease-specific patient-reported outcome (PRO) and health-related quality-of-life (HRQoL) measurements in patients with UC receiving tofacitinib in the OCTAVE clinical program.

Methods Analyses included patients from OCTAVE Open assigned to tofacitinib 5 mg twice daily (subpopulation in remission at Week 52 of OCTAVE Sustain). OCTAVE Open data from the final analyses are shown to Month 48. Endpoints included rectal bleeding subscore (RBS) = 0, stool frequency subscore (SFS) ≤ 1, and HRQoL measure, Inflammatory Bowel Disease Questionnaire (IBDQ) remission (IBDQ total score ≥ 170); with non-responder imputation for missing data at all visits, and last observation carried forward for visits after a patient advanced to the next study (NRI-LOCF). Observed cases were also assessed.

Results At Month 48, of 175 patients, 95 (54.3%) and 96 (54.9%) achieved/maintained RBS = 0 and SFS ≤ 1, respectively (NRI-LOCF). Additionally, 93 (53.1%) patients achieved/maintained IBDQ remission at Month 48 (NRI-LOCF).

Conclusions Among patients who entered OCTAVE Open in remission, most maintained normalization of rectal bleeding and improvement in stool frequency for ≤ 4 years of follow-up in OCTAVE Open. IBDQ remission was also generally maintained in OCTAVE Open. These data show robust maintenance of key UC PROs and durability of response with tofacitinib 5 mg twice daily.

Trial Registration http://www.ClinicalTrials.gov (NCT01465763 [21/10/2011]; NCT01458951 [21/10/2011]; NCT01458574 [21/10/2011]; NCT01470612 [21/10/2011]).

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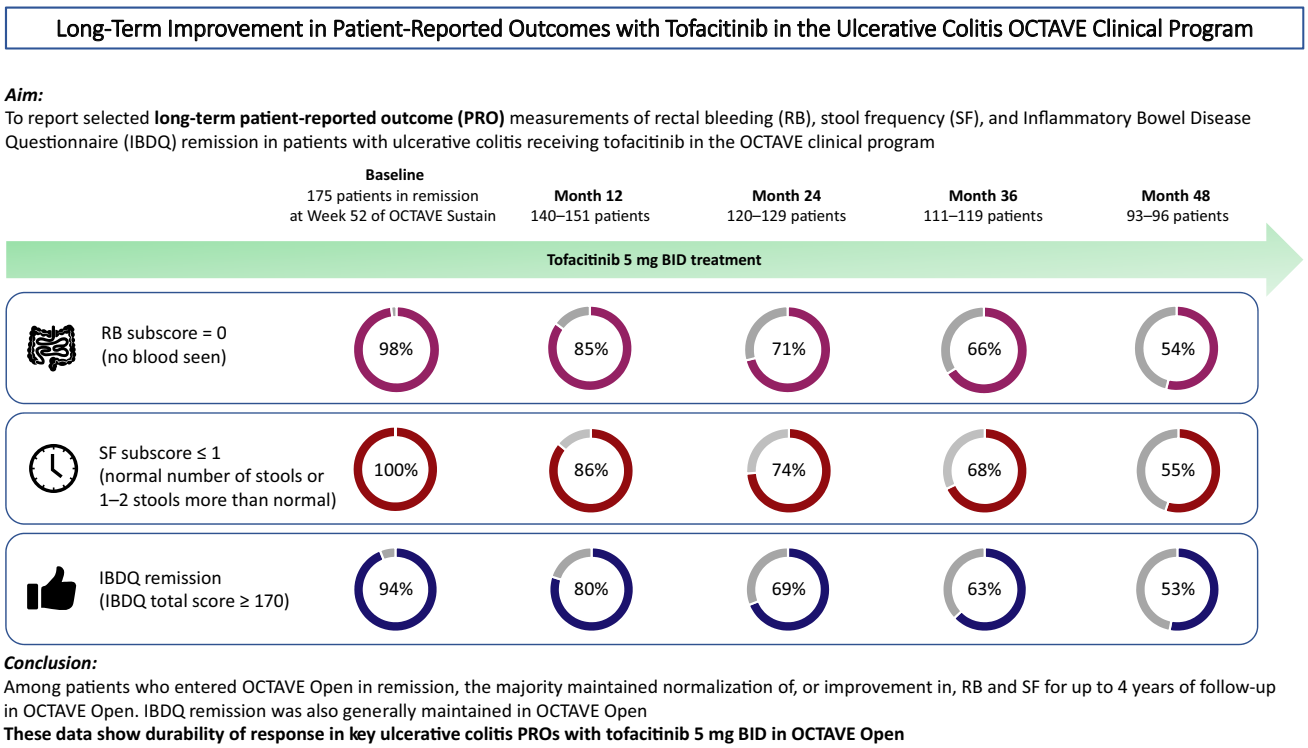
Graphical Abstract



Key Points for Decision Makers

Patients receiving tofacitinib 5 mg twice-daily maintenance therapy achieved consistent improvement in key measures of ulcerative colitis disease activity reported by patients, namely the severity of rectal bleeding and frequency of stools.

Improvement of physical symptoms was paired with improvement in quality of life related to health in patients receiving tofacitinib 5 mg twice daily.

Long-term management of ulcerative colitis symptoms can be achieved with the lower maintenance dose of tofacitinib 5 mg twice daily.

1 Introduction

Ulcerative colitis (UC) is a chronic, relapsing–remitting inflammatory disease of the colon [1], with rectal bleeding and increased stool frequency as hallmark symptoms [2]. Patient-reported outcomes (PROs) are self-administered assessments of disease activity without interpretation by a clinician and are a primary method to assess symptomatic relief. The rectal bleeding subscore (RBS) and stool frequency subscore (SFS), which are part of the overall Mayo score to assess disease activity, are commonly used PROs in randomized controlled trials and are being used more often in clinical practice [3].

Determining the durability of UC therapies to maintain symptomatic improvement in rectal bleeding and stool frequency is clinically important, as these outcome measures can be surrogates for overall endoscopic disease activity [4]. Moreover, rectal bleeding and stool frequency improvements are recognized as a goal in the treat-to-target strategy, which is described in the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-II guidelines [4, 5]. It has also been shown, through two global UC Narrative surveys completed by UC patients and physicians, that discussion of symptoms experienced since the previous visit is a top priority at appointments for both patients and physicians, and reduction of symptoms is a top priority for patients' medication satisfaction [6, 7]. Additionally, it is known that UC negatively impacts health-related quality of life (HRQoL) [8]. Improvement in HRQoL alongside clinical response is a major long-term treatment goal of UC and is included as

a recommendation in the STRIDE-II treat-to-target strategy [5, 9]. Therefore, the long-term reporting of RBS and SFS PROs and HRQoL outcomes such as the Inflammatory Bowel Disease Questionnaire (IBDQ) are clinically relevant for both patients and physicians.

Tofacitinib is an oral small molecule Janus kinase (JAK) inhibitor for the treatment of UC. It is a first-generation inhibitor of JAK that has functional selectivity for JAK1 and JAK3 signaling over JAK2 [10]. The efficacy and safety of tofacitinib have been evaluated in three phase III, randomized, placebo-controlled studies (OCTAVE Induction 1 and 2 and OCTAVE Sustain) [11], and an open-label, long-term extension study (OCTAVE Open), in patients with moderately to severely active UC [12]. Previous post hoc analysis of the tofacitinib phase III induction studies demonstrated a significant improvement in RBS and SFS versus placebo within 3 days of treatment [13].

These post hoc analyses from the OCTAVE program explore the long-term effect of tofacitinib on PRO measurements, including RBS, SFS, and IBDQ, in patients with UC.

2 Methods

2.1 Patients and Study Design

All studies were registered on http://www.ClinicalTrials.gov (NCT01465763, NCT01458951, NCT01458574, and NCT01470612). Full details of OCTAVE Induction 1 and 2, OCTAVE Sustain, and OCTAVE Open study designs have been reported previously [11, 14]. Patients in OCTAVE Induction 1 and 2 received placebo or tofacitinib 10 mg twice daily for 8 weeks. Responders from OCTAVE Induction 1 and 2 could enter OCTAVE Sustain and were randomized to receive placebo, tofacitinib 5 mg twice daily, or tofacitinib 10 mg twice daily for 52 weeks. Patients in remission at Week 52 of OCTAVE Sustain were assigned to receive tofacitinib 5 mg twice daily in OCTAVE Open.

These analyses include patients who received tofacitinib 5 mg twice daily in OCTAVE Open, regardless of prior treatment in OCTAVE Sustain. This population was used for these analyses, as it was important to determine long-term PROs in patients receiving the lower maintenance dose of tofacitinib. These patients (per protocol) had clinical response at Week 8 of OCTAVE Induction 1 or 2 and completed Week 52 of OCTAVE Sustain in remission. Analyses from OCTAVE Induction 1 and 2 and OCTAVE Sustain were also performed and are presented here for additional context. Clinical response was defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, with a decrease in RBS of ≥1 point or an absolute RBS of 0 or 1. Remission was defined as a total Mayo score of ≤2, with no individual subscore >1 and an RBS of 0.

Inclusion and exclusion criteria have been described previously [11, 14]. Briefly, for patients to be eligible to enter the studies, they had to be ≥18 years of age with a diagnosis of UC for ≥4 months (phase III OCTAVE Induction 1 and 2) and have had moderately to severely active UC at induction program entry (defined as a total Mayo score of 6–12, with an RBS of 1–3 and an endoscopic subscore of 2 or 3) [11].

During OCTAVE Sustain and OCTAVE Open, tapering of oral corticosteroids was mandatory.

2.2 Efficacy Assessments

Efficacy endpoints analyzed were RBS = 0, SFS ≤ 1, SFS = 0, the composites of RBS = 0 and SFS ≤ 1, and partial Mayo score (PMS) remission (PMS ≤ 2 with no individual subscore >1). PMS (including RBS, SFS, and Physician Global Assessment [PGA] subscore) was assessed at baseline to Week 8 (also baseline of OCTAVE Sustain) of OCTAVE Induction 1 and 2; Week 4 to Week 52 of OCTAVE Sustain; and baseline and Months 1, 4, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, and 48 in OCTAVE Open. The total Mayo score (including RBS, SFS, PGA, and endoscopic subscore) was assessed at baseline and Week 8 of OCTAVE Induction 1 and 2; Week 24 and Week 52 of OCTAVE Sustain; and baseline and Months 2, 12, 24, and 36 of OCTAVE Open.

2.3 Health-Related Quality-of-Life (HRQoL) Assessments

HRQoL outcomes in OCTAVE Induction 1 and 2 and OCTAVE Sustain have been reported previously [15]. IBDQ remission was defined as an IBDQ total score of ≥170. The IBDQ provides a total score (ranging from 32 to 224; higher scores indicate a better HRQoL) and four domain scores: bowel symptoms (10 items, scored from 10 to 70), systemic symptoms (5 items, scored from 5 to 35), emotional function (12 items, scored from 12 to 84), and social function (5 items, scored from 5 to 35). The IBDQ was self-administered by patients at baseline, Week 4, and Week 8 of OCTAVE Induction 1 and 2, from Week 8 to Week 52 of OCTAVE Sustain, and at Months 2, 6, 12, 18, 24, 30, 36, and 48 of OCTAVE Open.

2.4 Statistical Analyses

In these post hoc analyses, proportions of patients with RBS = 0, SFS ≤ 1, and SFS = 0, PMS remission (PMS ≤ 2 with no individual subscore > 1), and IBDQ remission (total score of ≥ 170) were analyzed over time. Data from OCTAVE Induction 1 and 2 and OCTAVE Sustain were analyzed by non-responder imputation (NRI). For OCTAVE Open, NRI was applied after a patient discontinued, 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 stayed in the study; no imputation for missing data was applied for ongoing patients except NRI for intermittent missing data. Observed case data are also reported. The analyses of patients from OCTAVE Open included data up to Month 48, as follow-up data were limited (≤40 patients) beyond Month 60.

2.5 Correlation Analyses

Exploratory point-biserial correlation analyses were used to assess the correlation between HRQoL and efficacy outcomes at Week 8 of OCTAVE Induction 1 and 2, and Week 52 of OCTAVE Sustain. IBDQ total score was used as a dichotomous variable (<170 vs. ≥170), and efficacy outcomes, including RBS, SFS, and PMS, were used as continuous variables (observed cases).

2.6 Study Ethics and Patient Consent

All studies 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.

3 Results

3.1 Patients

In OCTAVE Open, 142 patients who were in remission at baseline (per protocol) after receiving 52 weeks of tofacitinib maintenance therapy in OCTAVE Sustain, and 21 patients in remission after receiving 52 weeks of place bo therapy, were assigned to receive tofacitinib 5 mg twice daily. An additional 12 patients were assigned to tofacitinib 5 mg twice daily as protocol deviations owing to reasons such as patient eligibility not being confirmed prior to enrollment or tofacitinib dosage changes being performed outside of the protocol guidelines, making a total of 175 patients.

Baseline demographics and clinical characteristics of the tofacitinib 5 mg twice-daily patient group of OCTAVE Open are shown in Table 1. The mean age of patients treated with tofacitinib 5 mg twice daily was 44.5 years (standard deviation [SD] 14.6), and at OCTAVE Open baseline, the mean total Mayo score was 1.2 (SD 0.9). In the tofacitinib 5 mg twice-daily patient group, 74 (42.3%) and 116 (66.3%) patients had prior tumor necrosis factor inhibitor (TNFi) exposure and immunosuppressant use, and 66 (37.7%) and 110 (62.9%) patients had TNFi and immunosuppressant failure, respectively.

Table 1 Baseline demographics and clinical characteristics of patients treated with tofacitinib 5 mg twice daily in OCTAVE Open

	Tofacitinib 5 mg twice daily [*N* = 175]
Sex	
Male	96 (54.9)
Age, years	
Mean (SD)	44.5 (14.6)
Race[a]	
White	136 (77.7)
Asian	25 (14.3)
Other	9 (5.1)
Unspecified	5 (2.9)
Duration of disease, years	
< 6	92 (52.6)
≥ 6	83 (47.4)
Extent of disease[b,c]	
Proctosigmoiditis[d]	38 (21.8)
Left-sided colitis[e]	56 (32.2)
Extensive/pancolitis	80 (46.0)
Total Mayo score at baseline	
Mean (SD)	1.2 (0.9)
Prior TNFi exposure[b]	74 (42.3)
Prior TNFi failure[b]	66 (37.7)
Prior immunosuppressant use[b]	116 (66.3)
Prior immunosuppressant failure[b]	110 (62.9)
Prior TNFi and immunosuppressant failure[b]	51 (29.1)

Data are expressed as *n* (%) unless otherwise specified

Twelve patients not in remission at OCTAVE Open baseline were assigned tofacitinib 5 mg twice daily as protocol deviations. One patient was receiving oral corticosteroids at OCTAVE Open baseline

N number of patients treated in each treatment group, *n* number of patients within the given category, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitor

[a]No Black patients were included in this patient population

[b]Data were collected at baseline of OCTAVE Induction 1 and 2

[c]*N* = 174

[d]Proctosigmoiditis was defined as disease limited to the rectum and sigmoid

[e]Left-sided colitis was defined as disease extending beyond the sigmoid but not involving the entire colon

The number of patients assigned to treatment in OCTAVE Induction 1 and 2, and OCTAVE Sustain, are described in Online Resource 1.

3.2 Rectal Bleeding and Stool Frequency Patient-Reported Outcomes (PROs) in the OCTAVE Clinical Program

At baseline of OCTAVE Open, in patients assigned to tofacitinib 5 mg twice-daily treatment who entered OCTAVE

Open in remission (per protocol), 172 (98.3%) and 175 (100%) had RBS = 0 and SFS ≤ 1, respectively. Based on NRI-LOCF, at Months 12, 24, 36, and 48, respectively, 149 (85.1%), 124 (70.9%), 115 (65.7%), and 95 (54.3%) patients maintained or achieved RBS = 0 (Fig. 1). Corresponding values based on observed cases were 149 (*N* = 158, 94.3%), 124 (*N* = 134, 92.5%), 109 (*N* = 117, 93.2%), and 86 (*N* = 92, 93.5%) patients (Fig. 1). Of the 142 patients who were in remission after receiving 52 weeks of tofacitinib 5 mg twice-daily maintenance therapy in OCTAVE Sustain, based on NRI-LOCF and observed cases, 142 (100%) patients had RBS = 0 at baseline of OCTAVE Open. At Month 48, based on NRI-LOCF and observed cases, respectively, 65 (45.8%) and 57 (*N* = 60, 95.0%) patients maintained RBS = 0.

At Months 12, 24, 36, and 48, respectively, 151 (86.3%), 129 (73.7%), 119 (68.0%), and 96 (54.9%) patients maintained or achieved SFS ≤ 1 (NRI-LOCF) [Fig. 2]. At Months 12, 24, 36, and 48, respectively, 151 (*N* = 158, 95.6%), 129 (*N* = 134, 96.3%), 114 (*N* = 117, 97.4%), and 88 (*N* = 92, 95.7%) patients maintained or achieved SFS ≤ 1 (observed) [Fig. 2]. Of the 142 patients who were in remission after receiving 52 weeks of tofacitinib 5 mg twice-daily maintenance therapy in OCTAVE Sustain, based on NRI-LOCF and observed cases, 142 (100%) patients had SFS ≤ 1 at baseline of OCTAVE Open. At Month 48, based on NRI-LOCF and observed cases, respectively, 70 (49.3%) and 58 (*N* = 60, 96.7%) patients maintained SFS ≤ 1.

The composite endpoints of RBS = 0 and SFS ≤ 1, based on NRI-LOCF, was achieved in 172 (98.3%) patients at baseline of OCTAVE Open and 84 (48.0%) patients at Month 48. Corresponding values, based on observed cases, were 172 (98.3%) and 84 (*N* = 92, 91.3%) patients.

At baseline of OCTAVE Open, in patients assigned to tofacitinib 5 mg twice-daily treatment, 113 (64.6%) had SFS = 0 (see Online Resource 2). SFS = 0 was achieved or maintained in 66 (37.7%; NRI-LOCF) and 61 (*N* = 92, 66.3%; observed) patients at Month 48 (see Online Resource 2). Furthermore, at baseline of OCTAVE Open, in patients assigned to tofacitinib 5 mg twice-daily treatment, 174 (99.4%) were in PMS remission (see Online Resource 3). PMS remission was achieved or maintained in 95 (54.3%; NRI-LOCF) and 87 (*N* = 92, 94.6%; observed) patients at Month 48 (see Online Resource 3).

Based on NRI at Week 8 of OCTAVE Induction 1 and 2, and Week 52 of OCTAVE Sustain, higher proportions of patients receiving tofacitinib 10 mg twice daily (and tofacitinib 5 mg twice daily in OCTAVE Sustain) achieved RBS = 0 and SFS ≤ 1 than among those receiving placebo (see Online Resources 4 and 5).

3.3 HRQoL PROs in the OCTAVE Clinical Program

In patients in OCTAVE Open assigned to tofacitinib 5 mg twice-daily treatment, 165 (94.3%) patients were in IBDQ remission at baseline (Fig. 3). Based on NRI-LOCF, by Month 48, 93 (53.1%) patients maintained or achieved IBDQ remission. Based on LOCF, the mean (SD) changes from baseline to Month 48 in the IBDQ bowel function, emotional status, systemic symptoms, and social function domains were −3.3 (10.1), −3.4 (10.4), −1.8 (5.1), and −1.7 (5.1), respectively. Based on observed cases, by Month 48, 87 (83.7%) patients were in IBDQ remission (Fig. 3) and the mean (SD) changes from baseline to Month 48 in the IBDQ bowel function, emotional status, systemic symptoms, and social function domains were −1.1 (8.1), −1.7 (8.3), −0.9 (4.1), and −0.8 (4.3), respectively. Of the 142 patients who were in remission after receiving 52 weeks of tofacitinib 5 mg twice-daily maintenance therapy in OCTAVE Sustain, based on NRI-LOCF and observed cases, 136 (95.8%) patients were in IBDQ remission at baseline of OCTAVE Open. At Month 48, based on NRI-LOCF and observed cases, respectively, 64 (45.1%) and 56 (*N* = 62; 90.3%) patients achieved or maintained IBDQ remission.

Based on NRI-LOCF at Week 8 of OCTAVE Induction 1 and 2, and Week 52 of OCTAVE Sustain, higher proportions of patients receiving tofacitinib 10 mg twice daily (and tofacitinib 5 mg twice daily in OCTAVE Sustain) were in IBDQ remission than among those receiving placebo (see Online Resources 4 and 5) [11].

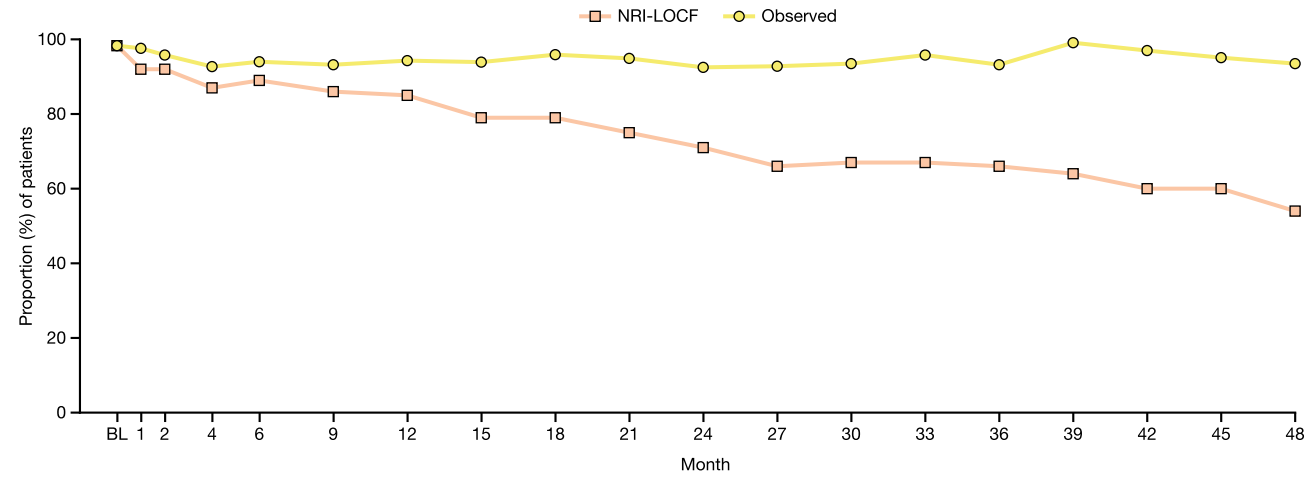
3.4 Correlation between Rectal Bleeding, Stool Frequency, Partial Mayo Score PROs, and Inflammatory Bowel Disease Questionnaire in the OCTAVE Program

Correlation analyses were conducted between IBDQ total score and RBS, SFS, and PMS. In OCTAVE Induction 1 and 2, RBS, SFS, and PMS had inverse correlations with IBDQ total score in patients treated with tofacitinib 10 mg twice daily or placebo (see Online Resource 6).

In OCTAVE Sustain, RBS, SFS, and PMS scores all had an inverse correlation with IBDQ total scores for all treatment groups (see Online Resource 7).

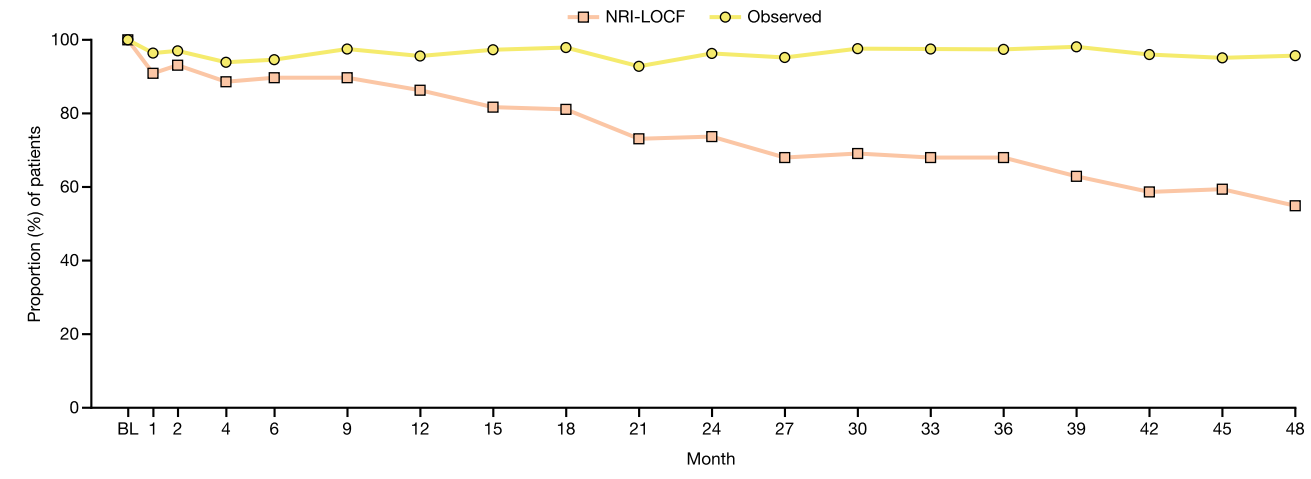
4 Discussion

We assessed the long-term effect of tofacitinib on rectal bleeding and stool frequency PROs, in addition to long-term disease-specific HRQoL (IBDQ) outcomes in the OCTAVE



		BL	1	2	4	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
NRI-LOCF	*n*	172	161	161	153	156	150	149	138	139	131	124	116	117	118	115	112	105	105	95
NRI-LOCF	*N*	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175
Observed	*n*	172	161	161	153	156	150	149	138	139	131	124	116	116	114	109	105	97	97	86
Observed	*N*	175	165	168	165	166	161	158	147	145	138	134	125	124	119	117	106	100	102	92

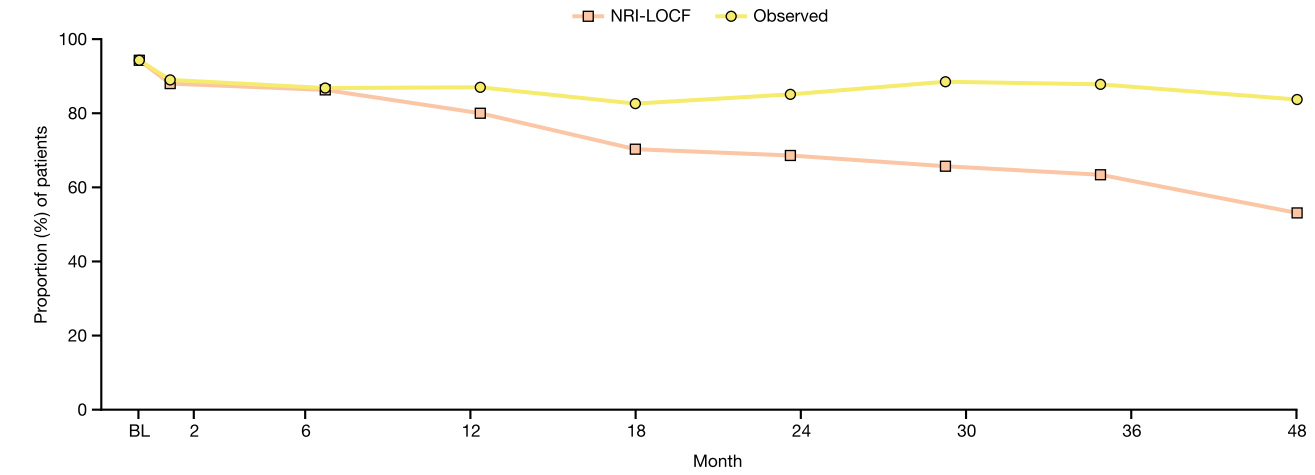
Fig. 1 Proportions of tofacitinib 5 mg twice daily-treated patients in remission at baseline with RBS = 0[a] in OCTAVE Open (FAS, NRI-LOCF, and observed). NRI was used for missing data at all visits and LOCF was used for visits after a patient advanced to the next study. [a]The RBS ranges from 0 to 3; an RBS of 0 equates to no blood seen, and the daily bleeding score represents the most severe bleeding of the day. *BL* baseline, *FAS* full analysis set, *N* number of patients treated in each treatment group, *n* number of patients with the specified response within the given category, *NRI-LOCF* non-responder imputation, last observation carried forward, *RBS* rectal bleeding subscore



		BL	1	2	4	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
NRI-LOCF	*n*	175	159	163	155	157	157	151	143	142	128	129	119	121	119	119	110	103	104	96
NRI-LOCF	*N*	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175	175
Observed	*n*	175	159	163	155	157	157	151	143	142	128	129	119	121	116	114	104	96	97	88
Observed	*N*	175	165	168	165	166	161	158	147	145	138	134	125	124	119	117	106	100	102	92

Fig. 2 Proportions of tofacitinib 5 mg twice daily-treated patients in remission at baseline with SFS ≤ 1[a] in OCTAVE Open (FAS, NRI-LOCF, and observed). NRI was used for missing data at all visits and LOCF was used for visits after a patient advanced to the next study. [a]The SFS ranges from 0 to 3; an SFS of 0 equates to a normal number of stools for the patient, and an SFS of 1 equates to one to two stools more than normal. Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency. Normal number of bowel movements represents the number of bowel movements when not having a flare. *BL* baseline, *FAS* full analysis set, *N* number of patients treated in each treatment group, *n* number of patients with the specified response within the given category, *NRI-LOCF* non-responder imputation, last observation carried forward, *SFS* stool frequency subscore

clinical program, complementing the previously completed studies demonstrating rapid response to tofacitinib treatment [13]. These analyses demonstrated that the majority of patients entering OCTAVE Open in remission achieved or maintained an RBS = 0 and SFS ≤ 1 up to Month 48 when receiving tofacitinib 5 mg twice daily. Importantly, for those



NRI-LOCF	*n*	165	154	151	140	123	120	115	111	93
NRI-LOCF	*N*	175	175	175	175	175	175	175	175	175
Observed	*n*	165	154	151	140	123	120	115	108	87
Observed	*N*	175	173	174	161	149	141	130	123	104

Fig. 3 Proportions of tofacitinib 5 mg twice daily-treated patients in remission at baseline with IBDQ remission[a] in OCTAVE Open (FAS, NRI-LOCF, and observed). NRI was used for missing data at all visits and LOCF was used for visits after a patient advanced to the next study. [a] IBDQ remission was defined as an IBDQ total score of ≥ 170. *BL* baseline, *FAS* full analysis set, *IBDQ* Inflammatory Bowel Disease Questionnaire, *N* number of patients treated in each treatment group, *n* number of patients with the specified response within the given category, *NRI-LOCF* non-responder imputation, last observation carried forward

patients who received tofacitinib treatment during OCTAVE Sustain, this time point represented at least 5 years of overall tofacitinib treatment in the OCTAVE clinical program.

More than half of patients who entered into OCTAVE Open in remission demonstrated continued normalization of rectal bleeding or improvement in stool frequency for 4 years. This is especially noteworthy, given that disease activity was moderate to severe (mean total Mayo scores ranging from 8.9 to 9.1) [11] for all patients entering the OCTAVE clinical program, and 66 (37.7%) patients in this OCTAVE Open subgroup had prior TNFi failure, which is considered a patient population more challenging to treat than a population without prior TNFi exposure [16].

The proportion of patients achieving or maintaining SFS = 0 was lower than those achieving or maintaining RBS = 0 or SFS ≤ 1. It is well known that normalization of stool frequency can be difficult to achieve [2]; one systematic review and meta-analysis suggested that patients in endoscopic remission were unlikely to have both an RBS and SFS of 0, with only 40% of patients in endoscopic remission achieving SFS = 0 and 36% showing a complete absence of symptoms [17]. The difficulty of achieving the complete normalization of stool frequency may be due to inflammation at the histological level [17], or due to remodeling of the colonic wall resulting from long-standing inflammation [18].

In addition to improvements in rectal bleeding and stool frequency, many patients achieved or maintained PMS remission at Month 48 of OCTAVE Open. Consistent with the Mayo score PRO components, IBDQ remission was also achieved or maintained in many patients at Month 48. Together, these results show the durability of the response to tofacitinib with regard to key UC PROs.

Induction and long-term maintenance of symptomatic remission defined by PROs remain important goals in the management of UC. To date, there have been few studies to demonstrate the long-term effect of UC therapies on rectal bleeding and stool frequency. The efficacy of the biologic therapy ustekinumab showed that the composite endpoint of RBS = 0 and SFS ≤ 1 was achieved by around 65% of patients up to Week 92 based on NRI analysis [19]. Our findings indicate that in OCTAVE Open, 95 (54.3%), 96 (54.9%), and 84 (48.0%) patients, respectively, achieved RBS = 0, SFS ≤ 1, and composite endpoints of RBS = 0 and SFS ≤ 1 at Month 48, based on NRI-LOCF analysis. Similarly, a post hoc analysis of the GEMINI 1 study of the integrin $\alpha_4\beta_7$, inhibitor, vedolizumab, in patients with UC found that at Week 52, RBS = 0 was achieved by 57% of patients, based on observed cases [20]. Moreover, observed data from a long-term extension study (which followed a 54-week or 30-week maintenance study) of patients with UC receiving infliximab showed that at the assessment at 1 year, 62% of patients had durability of response [21]. At Week 52 of OCTAVE Open, 94% of 5 mg twice daily-treated patients achieved RBS = 0. Although there have been no prospective

head-to-head studies comparing long-term efficacy of tofacitinib to infliximab, vedolizumab, or ustekinumab, our results are generally consistent with these other advanced therapies for moderate to severe UC.

An update of the 2015 STRIDE guidelines included new findings that acknowledge that restoration of quality of life is one of the most important long-term treatment targets for patients with UC [5]. Our analyses indicated that over half of patients receiving tofacitinib 5 mg twice-daily treatment who entered OCTAVE Open in remission (per protocol) remained in IBDQ remission at Month 48, consistent with the observed improvements in RBS and SFS. PMS remission was also maintained in the majority of patients at Month 48. It is noteworthy to recognize that PMS includes the PGA, representing a clinician-reported assessment of disease activity. In recently updated regulatory guidance, the PGA has been identified as a key limitation of the Mayo score, although it may still have relevance in practice management as it represents the clinician's perspective of their patient's disease activity [22]. Previous analyses have indicated that in patients treated with tofacitinib, early improvement in PGA subscore is consistent with improvements in the PROs of rectal bleeding and stool frequency [23].

The limitations of these analyses include that they are post hoc and that the self-reported nature of the endpoints of interest could be impacted by reference bias. Moreover, the majority of data were from the open-label, long-term extension study, which has inherent limitations. In addition, PROs that have been reported to be perceived as the most important by patients with UC, such as nausea, stool urgency, and pain [24, 25], were not analyzed in this study.

5 Conclusion

Overall, these data show durability of response with tofacitinib 5 mg twice daily, with robust and sustained normalization of rectal bleeding, and improvement in stool frequency for up to 4 years of follow-up in OCTAVE Open. This response was accompanied by long-term improvements in the IBDQ total score. As improving and resolving rectal bleeding and stool frequency in UC are defined therapeutic targets, these findings reiterate that maintenance treatment with tofacitinib 5 mg twice daily is appropriate for the long-term management of UC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40271-022-00603-w.

Acknowledgements This study was sponsored by Pfizer. The authors would like to thank the patients, investigators, and study teams involved in the tofacitinib UC clinical program. Medical writing support, under the direction of the authors, was provided by Caitlin Duncan, PhD, CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer Inc, New York, NY, USA, in accordance with Good Publication Practice (GPP 2022) guidelines [26].

Declarations

Funding This study was sponsored by Pfizer. Medical writing support was funded by Pfizer Inc.

Conflict of interest/competing interests David P. Hudesman has received research support from Janssen and Pfizer Inc; consulting fees from UCB; and personal fees from AbbVie, Bristol-Myers Squibb, Janssen, Pfizer Inc, Samsung, and Takeda. Joana Torres has received advisory board fees from Arena, Galapagos, Janssen, and Pfizer Inc; research support from AbbVie and Janssen; and lecture fees from Galapagos and Janssen. Leonardo Salese, John C. Woolcott, Rajiv Mundayat, and Chinyu Su are employees and stockholders of Pfizer Inc. Mahmoud H. Mosli has received research support from Takeda; and lecture fees from AbbVie, Hikma, Janssen, Pfizer Inc, and Takeda. Jessica R. Allegretti has received consulting fees from Artugen, Bacainn, Bristol-Myers Squibb, Celgene, Finch Therapeutics, Iterative Scopes, Janssen, Morphic, Pandion, and Pfizer Inc; and research support from Merck.

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.

Ethics approval All studies were conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. Study protocols were approved by the Institutional Review Boards and/or independent Ethics Committees at each of the investigational centers participating in the studies, or a central Institutional Review Board.

Consent to participate All patients provided written informed consent.

Consent for publication Not applicable.

Author contributions LS, JCW, RM, and CS contributed to the design of the post hoc analyses. RM performed the statistical analysis of the data. All authors contributed to the drafting and editing of the manuscript, and approved the final version of the article, including the authorship list.

References

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis. Lancet. 2017;389(10080):1756–70. https://doi.org/10.1016/S0140-6736(16)32126-2.
2. Colombel JF, Keir ME, Scherl A, Zhao R, de Hertogh G, Faubion WA, et al. Discrepancies between patient-reported outcomes, and endoscopic and histological appearance in UC. Gut. 2017;66(12):2063–8. https://doi.org/10.1136/gutjnl-2016-312307.
3. de Jong MJ, Huibregtse R, Masclee AAM, Jonkers DMAE, Pierik MJ. Patient-reported outcome measures for use in clinical trials and clinical practice in inflammatory bowel diseases: a systematic review. Clin Gastroenterol Hepatol. 2018;16(5):648-63.e3. https://doi.org/10.1016/j.cgh.2017.10.019.
4. Dulai PS, Singh S, Jairath V, Ma C, Narula N, Casteele NV, et al. Prevalence of endoscopic improvement and remission according to patient-reported outcomes in ulcerative colitis. Aliment Pharmacol Ther. 2020;51(4):435–45. https://doi.org/10.1111/apt.15577.
5. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology. 2021;160(5):1570–83. https://doi.org/10.1053/j.gastro.2020.12.031.
6. Rubin DT, Hart A, Panaccione R, Armuzzi A, Suvanto U, Deuring JJ, et al. Ulcerative Colitis Narrative global survey findings: communication gaps and agreements between patients and physicians. Inflamm Bowel Dis. 2021;27(7):1096–106. https://doi.org/10.1093/ibd/izaa257.
7. Dubinsky MC, Watanabe K, Molander P, Peyrin-Biroulet L, Rubin M, Melmed GY, et al. Ulcerative Colitis Narrative Global survey findings: the impact of living with ulcerative colitis—a patients' and physicians' view. Inflamm Bowel Dis. 2021;27(11):1747–55. https://doi.org/10.1093/ibd/izab016.
8. Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses-Part I. Inflamm Bowel Dis. 2018;24(4):742–51. https://doi.org/10.1093/ibd/izx100.
9. Ungaro R, Colombel J-F, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a systematic review. Am J Gastroenterol. 2019;114(6):874–83. https://doi.org/10.14309/ajg.0000000000000183.
10. Dowty ME, Lin TH, Jesson MI, Hegen M, Martin DA, Katkade V, et al. Janus kinase inhibitors for the treatment of rheumatoid arthritis demonstrate similar profiles of in vitro cytokine receptor inhibition. Pharmacol Res Perspect. 2019;7(6): e00537. https://doi.org/10.1002/prp2.537.
11. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376(18):1723–36. https://doi.org/10.1056/NEJMoa1606910.
12. Lichtenstein GR, Loftus EV Jr, Wei SC, Damião AO, Judd D, Lawendy N, et al. Tofacitinib, an oral, small-molecule Janus kinase inhibitor, in the treatment of ulcerative colitis: analysis of an open-label, long-term extension study with up to 5.9 years of treatment [abstract DOP61]. J Crohns Colitis. 2020;14(Supp 1):S100–1. https://doi.org/10.1093/ecco-jcc/jjz203.100.
13. Hanauer S, Panaccione R, Danese S, Cheifetz A, Reinisch W, Higgins PDR, et al. Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis. Clin Gastroenterol Hepatol. 2019;17:139–47. https://doi.org/10.1016/j.cgh.2018.07.009.
14. Colombel J-F, Osterman MT, Thorpe AJ, Salese L, Nduaka CI, Zhang H, et al. Maintenance of remission with tofacitinib therapy in patients with ulcerative colitis. Clin Gastroenterol Hepatol. 2022;20(1):116-25.e5. https://doi.org/10.1016/j.cgh.2020.10.004.
15. Panés J, Vermeire S, Lindsay JO, Sands BE, Su C, Friedman G, et al. Tofacitinib in patients with ulcerative colitis: health-related quality of life in Phase 3 randomised controlled induction and maintenance studies. J Crohns Colitis. 2018;12(2):145–56. https://doi.org/10.1093/ecco-jcc/jjx133.
16. Sands BE, Peyrin-Biroulet L, Marano C, O'Brien CD, Zhang H, Johanns J, et al. Efficacy in biologic failure and non-biologic-failure populations in a Phase 3 study of ustekinumab in moderate–severe ulcerative colitis: UNIFI [abstract P312]. J Crohns Colitis. 2019;13(Suppl 1):S256–7. https://doi.org/10.1093/ecco-jcc/jjy222.436.
17. Narula N, Alshahrani AA, Yuan Y, Reinisch W, Colombel JF. Patient-reported outcomes and endoscopic appearance of ulcerative colitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2019;17(3):411-8.e3. https://doi.org/10.1016/j.cgh.2018.06.015.
18. Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis as a progressive disease: the forgotten evidence. Inflamm Bowel Dis. 2012;18(7):1356–63. https://doi.org/10.1002/ibd.22839.
19. Panaccione R, Danese S, Sandborn WJ, O'Brien CD, Zhou Y, Zhang H, et al. Ustekinumab is effective and well tolerated for ulcerative colitis through 2 years of maintenance therapy. Aliment Pharmacol Ther. 2020;52(11–12):1658–75. https://doi.org/10.1111/apt.16119.
20. Feagan BG, Schreiber S, Wolf DC, Axler JL, Kaviya A, James A, et al. Sustained clinical remission with vedolizumab in patients with moderate-to-severe ulcerative colitis. Inflamm Bowel Dis. 2019;25(6):1028–35. https://doi.org/10.1093/ibd/izy323.
21. Reinisch W, Sandborn WJ, Rutgeerts P, Feagan BG, Rachmilewitz D, Hanauer SB, et al. Long-term infliximab maintenance therapy for ulcerative colitis: the ACT-1 and -2 extension studies. Inflamm Bowel Dis. 2012;18(2):201–11. https://doi.org/10.1002/ibd.21697.
22. Naegeli AN, Hunter T, Hoskin B, Middleton-Dalby C, Hetherington J, Stefani-Hunyady D, et al. Full, partial, and modified permutations of the Mayo score: characterizing clinical and patient-reported outcomes in ulcerative colitis patients. Crohns Colitis 360. 2021;3(1):otab007. https://doi.org/10.1093/crocol/otab007.
23. Chiorean M, Rubin DT, Löwenberg M, Gisbert JP, Tsilkos K, Quirk D, et al. Improvement in Physician's Global Assessment within 2 weeks in patients with ulcerative colitis treated with tofacitinib [abstract 734]. Am J Gastroenterol. 2018;113(Suppl):S419.
24. Nag A, Romero B. Development and content validation of patient-reported outcomes tools for ulcerative colitis and Crohn's disease in adults with moderate-to-severe disease. Health Qual Life Outcomes. 2022;20(1):75. https://doi.org/10.1186/s12955-022-01975-1.
25. Teich N, Schulze H, Knop J, Obermeier M, Stallmach A. Novel approaches identifying relevant patient-reported outcomes in patients with inflammatory bowel diseases—LISTEN 1. Crohn's & Colitis 360. 2021;3(3):otab050. https://doi.org/10.1093/crocol/otab050.
26. DeTora LM, Toroser D, Sykes A, Vanderlinden C, Plunkett FJ, Lane T, et al. Good Publication Practice (GPP) guidelines for company-sponsored biomedical research: 2022 update. Ann Intern Med. 2022;175(9):1298–304. https://doi.org/10.7326/M22-1460.