



Original Article

Tofacitinib in Patients with Ulcerative Colitis: Health-Related Quality of Life in Phase 3 Randomised Controlled Induction and Maintenance Studies

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Conference presentations: These data were presented at the 11th and 12th Congresses of European Crohn's and Colitis Organisation [ECCO 2016 and ECCO 2017] and at Digestive Disease Week [DDW] 2016 and DDW 2017.

Abstract

Background and Aims: Tofacitinib is an oral, small molecule Janus kinase [JAK] inhibitor that is being investigated for ulcerative colitis [UC]. We evaluated health-related quality of life [HRQoL] in tofacitinib UC Phase 3 studies.

Methods: Patients ≥ 18 years old in OCTAVE Induction 1 [N = 598] and 2 [N = 541] with moderately to severely active UC were randomised [1:4] to placebo or tofacitinib 10 mg twice daily [BID] for 8 weeks. Subsequently, OCTAVE Sustain re-randomised [1:1:1] clinical responders [N = 593] from induction studies to placebo, tofacitinib 5 mg BID, or 10 mg BID, for 52 weeks. Inflammatory Bowel Disease Questionnaire [IBDQ] and SF-36v2® Health Survey [SF-36v2] assessed HRQoL.

Results: In OCTAVE Induction 1 and 2, mean changes from baseline IBDQ were greater with tofacitinib 10 mg BID at Week 8 [40.7 and 44.6] versus placebo [21.0 and 25.0; $p < 0.0001$]; mean changes from baseline SF-36v2 Physical and Mental Component Summaries [PCS/MCS] were also greater with 10 mg BID [PCS: 6.8 and 6.8; MCS: 6.8 and 7.6] versus placebo [PCS: 2.5 and 4.6; MCS: 3.5 and 4.4; $p < 0.01$]. In OCTAVE Sustain at Week 52, changes in IBDQ were maintained with tofacitinib 5 mg [(+3.7] and 10 mg BID [4.8], and larger with placebo [-26.5; $p < 0.0001$]. Changes in SF-36v2 PCS/MCS were also maintained with 5 mg [PCS: 0.0; MCS: -1.0] and 10 mg BID [PCS: 0.3; MCS: 0.1] versus placebo [PCS: -5.2; MCS: -6.7; $p < 0.0001$] at Week 52 in OCTAVE Sustain.

Conclusions: Tofacitinib 10 mg BID induction therapy significantly improved HRQoL versus placebo at Week 8. Improvements were maintained through 52 weeks' maintenance therapy with tofacitinib 5 mg and 10 mg BID.

ClinicalTrials.gov registration numbers: NCT01465763, NCT01458951 and NCT01458574

Key Words: Patient-reported outcomes; quality of life; ulcerative colitis

1. Introduction

Ulcerative colitis [UC] is a chronic inflammatory disease of the colon characterised by alternating periods of relapse and remission.¹ Clinical features of UC include rectal bleeding, diarrhoea, abdominal pain, and urgency for defaecation. However, patients express concerns that go beyond just these physical symptoms. They report anxieties stemming from a lack of control over their bodily functions, fear of disease progression or hospitalisation, of colectomy, and of not having immediate access to a toilet.²⁻⁵ Physical symptoms and associated anxiety affect patients' employment opportunities and work productivity,^{3,4,6} limit their ability to engage in social and recreational activities,^{3-5,7,8} and may impair their ability to develop and maintain strong relationships with others, leading to difficulties in achieving intimacy, and feelings of isolation and depression.^{3,4,6} These experiences are concordant with findings that the presence and severity of physical symptoms have a significant impact on patients' health-related quality of life [HRQoL], including their functioning and well-being.^{9,10} Accordingly, treatments that demonstrate efficacy in improving clinical measures of disease can bring about improvements in HRQoL.¹¹⁻¹³

Patient-reported outcomes [PROs] have been recommended for inclusion in clinical trials assessing UC,¹⁴⁻¹⁷ as they directly reflect patient-perceived benefits of treatment.^{2,18} Findings, indicating that clinicians often underestimate the impact of UC symptoms on patients' functioning and well-being, support the importance of characterising and quantifying patients' perspectives to fully understand the effectiveness of UC treatments.^{19,20} In addition, patients, providers, payers, and regulators seek information on how patients feel and function in daily life, using well-defined, validated, and reliable assessments.²¹⁻²³

Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for UC. The efficacy and safety of tofacitinib for UC have been reported in a global Phase 2 dose-finding trial²⁴ and in Phase 3 induction [OCTAVE Induction 1 and 2] and maintenance [OCTAVE Sustain] studies.²⁵

The objective of these analyses was to evaluate the effect of tofacitinib on patients' HRQoL, using the disease-specific Inflammatory Bowel Disease Questionnaire [IBDQ] and the general Short Form-36v2® Health Survey [SF-36v2] during the OCTAVE induction and maintenance Phase 3 clinical trial programme. We hypothesised that patients with active UC who received 8 weeks of induction therapy with tofacitinib 10 mg BID would show greater improvement in IBDQ and SF-36v2 scores than with placebo. In addition, we hypothesised that clinical responders in the induction studies would maintain these improvements with tofacitinib 5 mg BID and tofacitinib 10 mg BID, whereas those receiving placebo would show loss in these improvements over 52 weeks of maintenance therapy.

2. Materials and Methods

2.1. Patients

OCTAVE Induction 1 [NCT01465763] and OCTAVE Induction 2 [NCT01458951] were identically designed, 8-week, randomised, double-blind, placebo-controlled studies. OCTAVE Induction 1 enrolled patients at 144 sites globally between April 2012 and May 2015. OCTAVE Induction 2 enrolled patients at 169 sites globally between June 2012 and April 2015.

Patients had to be aged ≥ 18 years and have a confirmed diagnosis of moderately to severely active UC for ≥ 4 months, defined by a Mayo score of 6–12, with a rectal bleeding subscore of 1–3 and an endoscopic subscore of 2–3. Eligibility was based on centrally read Mayo endoscopic subscores. Patients had to have previous failed treatment or to have demonstrated intolerance to treatment with at least one of the following therapies: corticosteroids, azathioprine, 6-mercaptopurine, infliximab, or adalimumab. Concomitant oral 5-aminosalicylates and oral corticosteroids [25 mg/day prednisone equivalent] were permitted in OCTAVE Induction 1 and 2, provided they were stably dosed throughout the study periods. Concomitant therapy with any anti-tumour necrosis factor [TNF] therapy [8-week washout period], azathioprine [2-week washout], methotrexate [2-week washout], and 6-mercaptopurine [2-week washout] was prohibited.

Patients who completed OCTAVE Induction 1 and 2 with clinical response [≥ 3 -point and $\geq 30\%$ decrease from baseline Mayo score, plus decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1] were eligible to participate in a 52-week tofacitinib maintenance study, OCTAVE Sustain [NCT01458574], which enrolled patients at 297 sites globally between July 2012 and May 2016. Steroid tapering was mandatory in OCTAVE Sustain, starting in the first week of the study. The tapering regime required all patients to be steroid free by Week 7.

2.2. Study design

The study designs of OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain have been reported previously.²⁵ Patients in OCTAVE Induction 1 and 2 were randomised [1:4] to treatment with placebo or tofacitinib 10 mg twice daily [BID] for 8 weeks. OCTAVE Induction 1 and 2 also included a tofacitinib 15 mg BID treatment arm, which was discontinued following a protocol amendment. Data from patients who received tofacitinib 15 mg BID in OCTAVE Induction 1 and 2 were analysed separately and are not reported in this manuscript. In OCTAVE Sustain, patients were re-randomised [1:1:1] to receive placebo, tofacitinib 5 mg BID, or tofacitinib 10 mg BID for 52 weeks. The randomisation and stratification of patients, and the results of primary efficacy and safety analyses, have been described previously.²⁵

2.3. PRO instruments

HRQoL was assessed using the disease-specific IBDQ 32-item questionnaire and generic SF-36v2 [acute form, 1-week recall]. The IBDQ provides a total score [range from 32 to 224; higher scores indicate 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].²⁶ Higher domain and total scores indicate better HRQoL. An increase in the IBDQ total score of ≥ 16 points from baseline corresponds to clinically meaningful IBDQ response, and an absolute IBDQ total score of ≥ 170 corresponds to IBDQ remission.^{27,28} The IBDQ was self-administered by patients at baseline, Week 4 and Week 8 in induction studies, and at Weeks 8 [ie 8 weeks post-baseline], 16, 24, 32, 40 and 52 in the maintenance study. IBDQ data at Week 8 of the induction studies were used as baseline values for the maintenance study.

The SF-36v2²⁹ assesses eight domains of functional health [physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health], scored from 0 to 100 and then standardised into norm-based *T*-scores with a mean of 50 and a standard deviation of 10 for the US general population. Scores from all domains are summarised as physical and mental component summary [PCS and MCS] scores, which are also expressed as *T*-scores. Higher domain and summary scores indicate better HRQoL. The SF-36v2 was self-administered by patients at baseline and Week 8 in induction studies, and at Weeks 24 and 52 in the maintenance study. SF-36v2 data at Week 8 of the induction studies were used as baseline values for the maintenance study.

2.4. Statistical analysis

2.4.1. Prespecified analyses

The primary efficacy endpoint in OCTAVE Induction 1 and 2 was Week 8 remission, based on Mayo score criteria [Mayo score ≤ 2 , no subscore > 1 , and rectal bleeding subscore of 0]. In OCTAVE Sustain, the primary efficacy endpoint was remission at Week 52.

In this manuscript, we report the following analyses, based on IBDQ and SF-36v2, that were prespecified secondary analyses in OCTAVE Induction 1 and 2 and OCTAVE Sustain: changes from baseline in IBDQ total score and domain scores over time; the proportions of patients with IBDQ remission and IBDQ response over time [IBDQ response was a prespecified endpoint in OCTAVE Induction 1 and 2 only]; the proportion of patients achieving improvement in IBDQ bowel symptom domain, which was prespecified in OCTAVE Induction 1 and 2 [increase of at least 1.2 points from baseline in average item score among IBDQ bowel symptom domain];^{26,30} and scores and changes from baseline in SF-36v2 individual domain scores, PCS, and MCS over time. Data are presented for the full analysis set, which included all patients randomised to placebo, tofacitinib 5 mg BID [OCTAVE Sustain only], and tofacitinib 10 mg BID.

Binary endpoints were compared using the Cochran-Mantel-Haenszel chi-square test, stratified by: previous treatment with anti-TNF, steroid use at baseline and geographical region for OCTAVE Induction 1 and 2; and by remission status at baseline of OCTAVE Sustain, and treatment assignment in induction study for OCTAVE Sustain. Patients with missing data were treated as non-responders. Continuous endpoints based on IBDQ scores were analysed using linear mixed-effects [LME] models based on all available [observed case] data. In OCTAVE Induction 1 and 2, baseline, treatment group, previous treatment with anti-TNF agents, steroid use at baseline, geographical region, visit, and treatment group by visit interaction were treated as fixed effects and subject as a random effect in LME models. In OCTAVE Sustain, baseline of maintenance study, treatment group, remission status at baseline of OCTAVE Sustain, treatment assignment in induction study, visit, and treatment group by visit interaction were treated as fixed effects, and subject as a random effect in LME models. Continuous endpoints based on SF-36v2 were analysed using analysis of covariance models in induction studies [with treatment group, previous treatment with anti-TNF therapy, steroid use at baseline, and geographical region as factors, and baseline as a covariate] and LME models in maintenance studies [with fixed and random effects as above for continuous endpoints based on IBDQ], both based on observed case data.³¹ Least squares [LS] mean changes from baseline IBDQ total scores, IBDQ domain scores, SF-36v2 domain scores, and SF-36v2 PCS and MCS scores were calculated using these models. In OCTAVE Induction 1 and 2, LME models were used to analyse IBDQ scores and ANCOVA to analyse SF-36v2 scores, as IBDQ scores were collected at more than two visits whereas SF-36v2 scores were collected at only two visits.

2.4.2. Post hoc analysis of subgroups and correlation between HRQoL and clinical efficacy data

Subgroup analyses were conducted for changes from baseline in IBDQ total score, proportions of patients with IBDQ remission and IBDQ response, and changes from baseline in SF-36v2 PCS and MCS scores. Subgroups evaluated were corticosteroid use at baseline [yes/no], gender [male/female], and previous anti-TNF therapy [yes/no]. For OCTAVE Induction 1 and 2, pooled data are presented for subgroup analyses.

Analyses were conducted to evaluate correlation between HRQoL endpoints [IBDQ total score, IBDQ remission, IBDQ response, and SF-36v2 PCS and MCS], and clinical efficacy endpoints (remission and mucosal healing [Mayo endoscopic subscore ≤ 1]) at Week 8 in OCTAVE Induction 1 and 2 [pooled data] and at Week 52 in OCTAVE Sustain. For IBDQ remission and IBDQ response, the numbers and proportions of patients with responses were calculated for patients with and without remission, and with and without mucosal healing. For IBDQ total score, and SF-36v2 PCS and MCS, mean score and standard deviation were calculated for patients with and without remission and with and without mucosal healing. Pearson correlation coefficients were calculated and differences in proportions or means for patients with and without remission and mucosal healing were calculated, along with 95% confidence intervals and *p*-values based on chi-square test [IBDQ remission and response] and *T*-test [IBDQ total score and SF-36v2 PCS and MCS].

2.4.3. Post hoc analysis of SF-36v2 scores versus age-/gender-matched norms

To supplement the analyses based on SF-36v2, a *post hoc* analysis evaluating HRQoL, as measured by SF-36v2, with tofacitinib induction therapy and maintenance therapy was performed. The objective of this analysis was to assess the burden of UC on HRQoL by examining deficits in SF-36v2 scores of patients in the OCTAVE trials relative to those in the general population. The same models [as in the prespecified analyses] were used, with the only difference being that SF-36v2 domain scores were used as outcomes instead of change from baseline in the SF-36v2 domain scores. Age- and gender-matched normative SF-36v2 domain and component scores [normed to, and based on, a representative US general population sample]³² were estimated based on the age and gender distribution of all available patients at baseline of OCTAVE Induction 1 and 2 and OCTAVE Sustain, and compared versus mean SF-36v2 domain and component scores at baseline and Week 8 [OCTAVE Induction 1 and 2], and baseline and Week 52 [OCTAVE Sustain].

2.5. Study ethics and patient consent

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

3. Results

3.1. Patients

In OCTAVE Induction 1, 614 patients were randomised [122 received placebo, 476 received tofacitinib 10 mg BID, and 16 received tofacitinib 15 mg BID]. OCTAVE Induction 2 randomised 547 patients [112 received placebo, 429 received tofacitinib 10 mg BID, and six received tofacitinib 15 mg BID]. In OCTAVE Sustain, 593 patients who were clinical responders in induction studies were

Table 1. Baseline demographics and disease characteristics in OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain.

	OCTAVE Induction 1		OCTAVE Induction 2		OCTAVE Sustain		
	Placebo [N = 122]	Tofacitinib 10 mg BID [N = 476]	Placebo [N = 112]	Tofacitinib 10 mg BID [N = 429]	Placebo [N = 198]	Tofacitinib 5 mg BID [N = 198]	Tofacitinib 10 mg BID [N = 197]
Age, mean years, [SD]	41.8 [15.3]	41.3 [14.1]	40.4 [13.2]	41.1 [13.5]	43.4 [14.0] ^a	41.9 [13.7] ^a	42.9 [14.4] ^a
Gender, N [%] male	77 [63.1]	277 [58.2]	55 [49.1]	259 [60.4]	116 [58.6]	103 [52.0]	110 [55.8]
Duration of disease, median years [range]	6.0 [0.5–36.2]	6.5 [0.3–42.5]	6.2 [0.4–27.9]	6.0 [0.4–39.4]	7.2 [0.6–42.7]	6.5 [0.6–40.3]	6.8 [0.6–35.7]
Previous anti-TNF therapy, N [%]	65 [53.3]	254 [53.4]	65 [58.0]	234 [54.5]	92 [46.5] ^a	90 [45.5] ^a	101 [51.3] ^a
Concomitant aminosalicylates, N [%]	90 [73.8]	336 [70.6]	76 [67.9]	312 [72.7]	148 [74.7]	144 [72.7]	142 [72.4]
Concomitant corticosteroids, N [%]	58 [47.5]	214 [45.0]	56 [50.0]	202 [47.1]	105 [53.0]	103 [52.0]	91 [46.4]
Mayo score, mean [SD]	9.1 [1.4]	9.0 [1.4]	8.9 [1.5]	9.0 [1.5]	3.3 [1.8]	3.3 [1.8]	3.4 [1.8]
IBDQ total score, mean [SD]	124.9 [33.2]	123.2 [33.3]	117.5 [28.5]	120.0 [30.7]	181.3 [28.3]	182.1 [28.7]	182.3 [27.9]
IBDQ domain scores, mean [SD]							
Bowel function	38.3 [9.3]	37.5 [9.7]	35.6 [8.1]	36.4 [8.9]	58.2 [8.6]	58.7 [8.9]	58.4 [8.4]
Systemic symptoms	18.2 [5.6]	18.0 [6.0]	16.9 [5.2]	17.4 [5.7]	26.1 [5.3]	26.5 [5.2]	26.7 [4.9]
Emotional status	48.9 [14.5]	48.5 [14.0]	46.3 [12.9]	47.5 [13.5]	66.9 [12.3]	67.0 [11.8]	67.5 [11.5]
Social function	19.5 [7.8]	19.2 [7.7]	18.7 [6.9]	18.6 [7.2]	30.1 [5.7]	30.0 [5.9]	29.7 [5.8]
SF-36v2 PCS, mean [SD]	41.5 [8.0]	41.2 [8.3]	40.2 [7.6]	40.5 [8.2]	50.0 [7.2]	50.5 [6.8]	49.3 [7.1]
SF-36v2 MCS, mean [SD]	38.7 [12.0]	39.0 [12.0]	38.3 [11.2]	37.8 [11.2]	47.8 [10.6]	49.0 [9.3]	48.9 [9.6]
SF-36v2 domain scores, mean [SD]							
Physical function	46.0 [8.4]	45.7 [8.8]	44.9 [8.9]	45.2 [9.1]	51.8 [6.9]	52.3 [6.7]	51.2 [7.2]
Role physical	37.8 [10.2]	37.8 [10.8]	36.7 [10.4]	36.6 [10.1]	48.9 [8.7]	49.5 [8.5]	48.5 [8.9]
Bodily pain	41.6 [10.0]	41.7 [10.7]	39.9 [8.5]	40.3 [9.5]	52.6 [9.1]	52.9 [8.6]	51.9 [9.3]
General health	35.3 [9.2]	34.7 [8.5]	34.9 [7.2]	34.5 [8.1]	42.3 [9.4]	43.3 [8.9]	42.9 [9.3]
Vitality	40.9 [10.3]	40.6 [10.4]	39.2 [9.4]	39.0 [9.8]	51.4 [10.0]	52.4 [8.5]	51.8 [9.4]
Social functioning	36.5 [11.8]	36.5 [12.0]	35.9 [10.7]	35.5 [11.0]	47.9 [9.9]	49.3 [8.9]	48.4 [9.0]
Role emotional	39.4 [12.3]	40.6 [13.2]	39.9 [12.8]	39.4 [12.3]	47.9 [10.2]	48.9 [9.5]	48.6 [9.2]
Mental health	40.7 [11.4]	40.5 [11.5]	39.8 [11.1]	39.5 [11.2]	48.5 [10.6]	49.4 [9.6]	49.4 [9.5]

BID, twice daily; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; SD, standard deviation; SF-36v2, Short Form-36v2 Health Survey; TNF, tumour necrosis factor; UC, ulcerative colitis.

^aAt induction study baseline. All other baseline values presented for OCTAVE Sustain are at randomisation into the maintenance study.

re-randomised [198 received placebo, 198 received tofacitinib 5 mg BID, and 197 received tofacitinib 10 mg BID] into the maintenance study. Full details of patient disposition and demographics have been reported previously [see supplementary material for details of patient disposition, available as Supplementary data at ECCO-JCC online].²⁵

3.2. IBDQ

Mean IBDQ total score ranged from 117.5 to 124.9 across treatment groups at baseline of OCTAVE Induction 1 and 2 [Table 1]. In both OCTAVE Induction 1 and 2, treatment with tofacitinib 10 mg BID resulted in statistically significant improvements from baseline in mean IBDQ total score versus placebo at Week 4 and Week 8 [$p < 0.0001$ for all comparisons; Figure 1A and B]. At Week 8 of OCTAVE Induction 1 and 2, LS mean changes from baseline IBDQ total score

with tofacitinib 10 mg BID were 40.7 and 44.6, respectively, versus 21.0 and 25.0 with placebo, respectively. Statistically significant [$p < 0.0001$ for all comparisons at Week 4 and Week 8] improvements in mean changes from baseline in all four IBDQ domain scores were seen with tofacitinib 10 mg BID versus placebo in both OCTAVE Induction 1 and 2 [Table 2]. Treatment effect was observed regardless of whether patients were receiving corticosteroids at baseline, of gender, and of previous anti-TNF therapy [see Supplementary Table 1, available as Supplementary data at ECCO-JCC online].

Mean IBDQ total scores at baseline of OCTAVE Sustain ranged from 181.3 to 182.3 across treatment groups. LS mean changes from baseline in IBDQ total score were maintained [with respect to baseline of OCTAVE Sustain] with tofacitinib 5 mg BID and tofacitinib 10 mg BID compared with placebo at all time points [$p < 0.0001$ for all comparisons; Figure 1C]. At Week 52, LS mean changes from

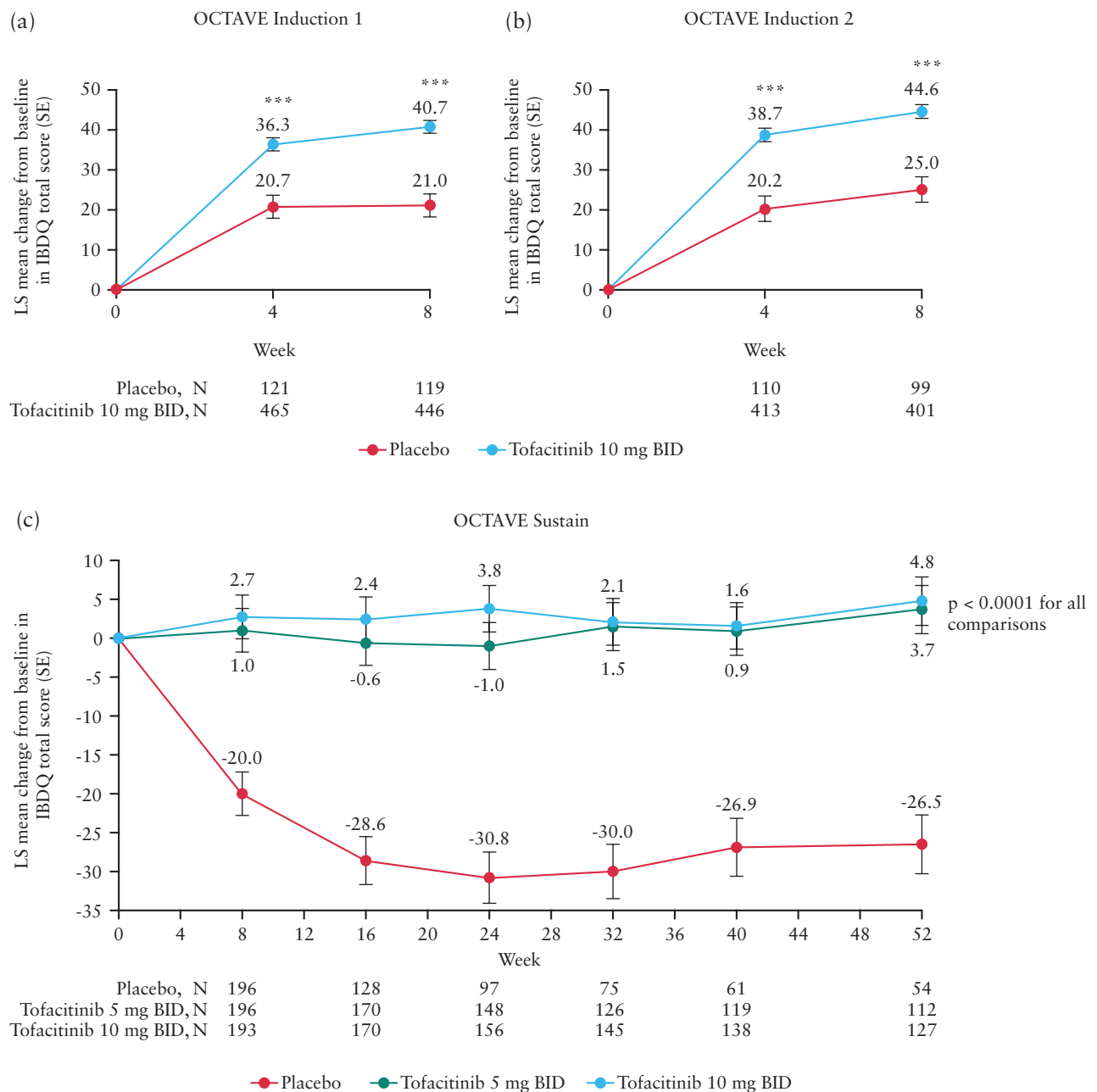


Figure 1. LS mean change from baseline in IBDQ total score over time in [A] OCTAVE Induction 1, [B] OCTAVE Induction 2, and [C] OCTAVE Sustain. BID, twice daily; IBDQ, Inflammatory Bowel Disease Questionnaire; LME, linear mixed-effects; LS, least squares; SE, standard error. *** $p < 0.0001$ versus placebo; data are full analysis set, observed case, using LME model.

Table 2. LS mean changes from baseline in IBDQ domain scores over time in OCTAVE Induction 1 and 2.

	OCTAVE Induction 1		OCTAVE Induction 2	
	Placebo [N = 122]	Tofacitinib 10 mg BID [N = 476]	Placebo [N = 112]	Tofacitinib 10 mg BID [N = 429]
LS mean change from baseline in IBDQ domain scores, mean [SE]				
Bowel function				
Week 4	7.6 [1.0]	13.4 [0.5]***	7.2 [1.1]	14.0 [0.6]***
Week 8	8.0 [1.0]	14.9 [0.5]***	9.4 [1.1]	16.1 [0.6]***
Systemic symptoms				
Week 4	3.1 [0.5]	5.2 [0.3]***	2.9 [0.5]	6.0 [0.3]***
Week 8	3.0 [0.5]	5.9 [0.3]***	3.8 [0.5]	6.8 [0.3]***
Emotional status				
Week 4	6.6 [1.1]	11.5 [0.6]***	6.9 [1.2]	12.2 [0.6]***
Week 8	6.8 [1.1]	12.6 [0.6]***	8.4 [1.2]	14.1 [0.7]***
Social function				
Week 4	3.5 [0.6]	6.3 [0.3]***	3.1 [0.6]	6.6 [0.4]***
Week 8	3.4 [0.6]	7.4 [0.3]***	3.5 [0.7]	7.7 [0.4]***

BID, twice daily; IBDQ, Inflammatory Bowel Disease Questionnaire; LME, linear mixed-effects; LS, least squares; SE, standard error.

*** $p < 0.0001$ versus placebo; data are full analysis set, observed case, using LME model.

Table 3. LS mean changes from baseline in IBDQ domain scores over time in OCTAVE Sustain.

	OCTAVE Sustain		
	Placebo [N = 198]	Tofacitinib 5 mg BID [N = 198]	Tofacitinib 10 mg BID [N = 197]
LS mean change from baseline in IBDQ domain scores, mean [SE]			
Bowel function			
Week 8	-7.9 [1.0]	-0.1 [1.0]***	0.0 [1.0]***
Week 24	-10.9 [1.1]	-1.8 [1.0]***	0.5 [1.0]***
Week 52	-9.4 [1.3]	-0.3 [1.1]***	0.8 [1.1]***
Systemic symptoms			
Week 8	-3.0 [0.4]	-0.2 [0.4]***	-0.1 [0.4]***
Week 24	-4.0 [0.5]	-0.0 [0.5]***	0.4 [0.5]***
Week 52	-3.4 [0.6]	0.9 [0.5]***	0.6 [0.5]***
Emotional status			
Week 8	-6.2 [1.0]	0.3 [1.0]***	1.6 [1.0]***
Week 24	-10.4 [1.2]	0.4 [1.1]***	1.9 [1.1]***
Week 52	-8.9 [1.4]	2.1 [1.2]***	2.2 [1.1]***
Social function			
Week 8	-3.1 [0.5]	0.9 [0.5]***	0.9 [0.5]***
Week 24	-4.9 [0.6]	0.5 [0.6]***	1.0 [0.6]***
Week 52	-4.1 [0.7]	1.1 [0.6]***	1.3 [0.6]***

BID, twice daily; IBDQ, Inflammatory Bowel Disease Questionnaire; LME, linear mixed-effects; LS, least squares; SE, standard error.

*** $p < 0.0001$ versus placebo; data are full analysis set, observed case, using LME model.

baseline in IBDQ total scores were 3.7 and 4.8 with tofacitinib 5 mg BID and tofacitinib 10 mg BID, respectively, versus -26.5 with placebo. Mean changes from baseline IBDQ domain scores were also maintained with both doses of tofacitinib compared with placebo at all time points measured [$p < 0.0001$ for all comparisons including Weeks 16, 32, and 40 [data not shown]; data for Weeks 8, 24, and 52 are shown in Table 3]. A treatment effect was observed across all subgroups evaluated [see Supplementary Table 2, available as Supplementary data at ECCO-JCC online].

The proportions of patients achieving IBDQ remission and IBDQ response in OCTAVE Induction 1 and 2 and OCTAVE Sustain were reported previously.²⁵ A significantly greater proportion of patients achieved IBDQ remission and response with tofacitinib 10 mg BID versus placebo at Week 4 and Week 8 in both OCTAVE Induction 1 and 2 [$p < 0.01$ for all comparisons].²⁵

A treatment effect was observed across all subgroups evaluated [see Supplementary Table 3, available as Supplementary data at ECCO-JCC online]. Significantly more patients achieved improvement in IBDQ bowel symptoms domain with tofacitinib 10 mg BID versus placebo at Week 4 and Week 8 in both OCTAVE Induction 1 and 2 [$p < 0.01$; Figure 2].

At baseline of OCTAVE Sustain, 70.2% [$n/N = 139/198$] of patients in the placebo group, 75.3% [149/198] of patients in the tofacitinib 5 mg BID group, and 72.1% [142/197] of patients in the tofacitinib 10 mg BID group were in IBDQ remission. This IBDQ remission was maintained by significantly greater proportions of patients receiving either dose of tofacitinib versus placebo throughout OCTAVE Sustain [$p < 0.0001$ for all comparisons].²⁵ At baseline of OCTAVE Sustain, 89.9% [$n/N = 178/198$] of patients in the placebo group, 92.4% [183/198] of patients in the tofacitinib 5 mg BID group, and 91.4%

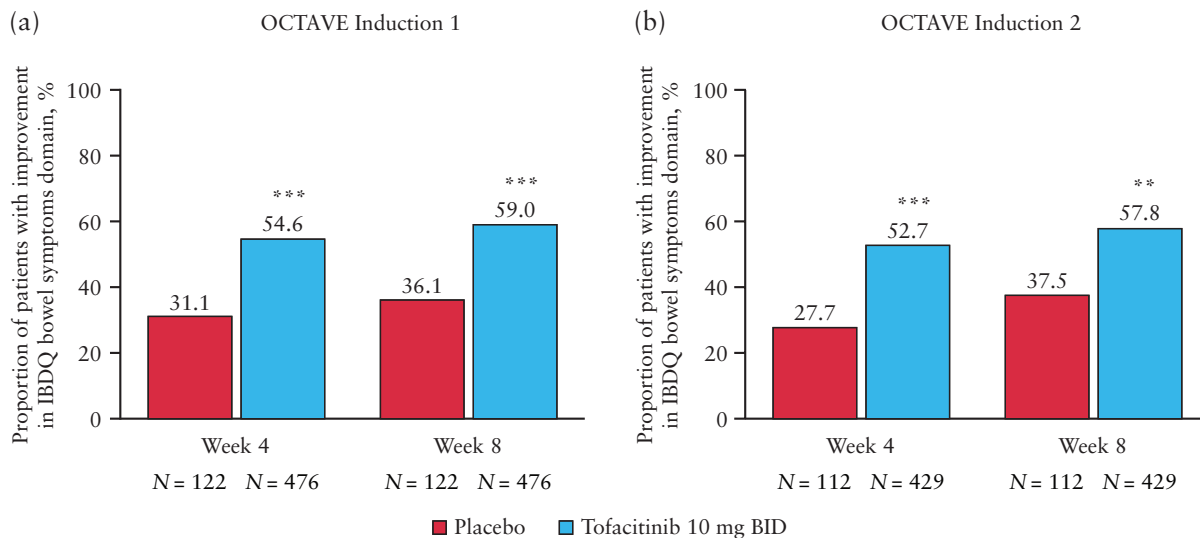


Figure 2. Proportion of patients achieving improvement in IBDQ bowel symptoms domain in OCTAVE Induction 1 and 2. BID, twice daily; IBDQ, Inflammatory Bowel Disease Questionnaire. ** $p < 0.01$, *** $p < 0.0001$ versus placebo; data are full analysis set with non-responder imputation; improvement in IBDQ bowel symptom domain was defined by an increase of at least 1.2 from baseline in average item score among IBDQ bowel symptom domain.

[180/197] of patients in the tofacitinib 10 mg BID group had IBDQ response [with respect to induction study baseline]. At all visits of OCTAVE Sustain, IBDQ response was maintained by significantly more patients receiving either dose of tofacitinib than placebo [$p < 0.0001$ for all comparisons].²⁵ A treatment effect was observed across all subgroups evaluated [see Supplementary Table 4, available as Supplementary data at *ECCO-JCC* online].

3.3. SF-36v2

At baseline of OCTAVE Induction 1 and 2, mean SF-36v2 PCS and MCS scores ranged from 40.2 to 41.5 and 37.8 to 39.0, respectively, across treatment groups. At Week 8, LS mean improvements from baseline in SF-36v2 PCS and MCS were significantly greater with tofacitinib 10 mg BID versus placebo in OCTAVE Induction 1 [PCS, $p < 0.0001$; MCS, $p < 0.01$; **Figure 3A**] and OCTAVE Induction 2 [PCS, $p < 0.01$; MCS, $p < 0.01$; **Figure 3B**]. A treatment effect was observed across all subgroups evaluated [see Supplementary Table 5, available as Supplementary data at *ECCO-JCC* online]. Significantly greater improvements were observed in LS mean change from baseline across all SF-36v2 domain scores with tofacitinib 10 mg BID versus placebo at Week 8 [$p \leq 0.05$ for all comparisons; **Table 4**].

Mean SF-36v2 PCS and MCS at baseline of OCTAVE Sustain ranged from 49.3 to 50.5 and 47.8 to 49.0, respectively. At Week 24 and Week 52 of OCTAVE Sustain, LS mean changes from baseline in SF-36v2 PCS and MCS were maintained [with respect to baseline of OCTAVE Sustain] with both tofacitinib 5 mg BID and tofacitinib 10 mg BID compared with placebo [$p < 0.0001$ for all comparisons; **Figure 3C**]. A treatment effect was observed across all subgroups evaluated [see Supplementary Table 6, available as Supplementary data at *ECCO-JCC* online]. Mean changes from baseline SF-36v2 domain scores were also maintained with both doses of tofacitinib compared with placebo at Weeks 24 and 52 [$p < 0.01$ for all comparisons; **Table 5**].

3.4. Correlation analyses between HRQoL endpoints and clinical efficacy endpoints

At Week 8 of OCTAVE Induction 1 and 2, significant correlations were observed between HRQoL endpoints and remission and mucosal

healing clinical efficacy endpoints, with greater efficacy observed for IBDQ total score, IBDQ remission, IBDQ response, and SF-36v2 PCS and MCS for patients in remission and patients with mucosal healing, compared with those not in remission and without mucosal healing [see Supplementary Table 7, available as Supplementary data at *ECCO-JCC* online]. Significant correlations were also observed at Week 52 in OCTAVE Sustain between all HRQoL endpoints and remission and mucosal healing clinical efficacy [see Supplementary Table 8, available as Supplementary data at *ECCO-JCC* online].

3.5. Post hoc analysis of SF-36v2 scores versus age- and gender-matched norms

At baseline of OCTAVE Induction 1 and 2, differences between mean SF-36v2 domain, PCS and MCS scores, and age-/gender-matched norms indicated the burden of disease in the study populations compared with the general population [**Figure 4A** and **C**]. Differences following 8 weeks of therapy were smaller [more favourable] with tofacitinib 10 mg BID than with placebo [**Figure 4B** and **D**], reflecting a movement towards normalisation of HRQoL with tofacitinib induction therapy [note that in this analysis a difference of 0 or a negative value indicated normalisation of HRQoL; a positive value indicated HRQoL burden with respect to age- and gender-matched norms].

In OCTAVE Sustain, baseline differences between mean SF-36v2 domain, PCS and MCS scores, and age-/gender-matched norms were smaller than at baseline of OCTAVE Induction 1 and 2 [and in some cases negative], reflecting improvements in HRQoL gained during OCTAVE Induction 1 and 2 [**Figure 4E**]. Patients treated with either dose of tofacitinib in OCTAVE Sustain generally maintained SF-36v2 scores [with the exception of the General health domain] close to the age-/gender-matched norms following 52 weeks of treatment, as the difference between mean SF-36v2 scores and age-/gender-matched norms was relatively small [**Figure 4F**], suggesting essentially a normalisation of their quality of life. For patients treated with placebo, the difference between mean SF-36v2 scores and age-/gender-matched norms at Week 52 was consistently and noticeably greater than that observed with tofacitinib 5 mg BID and 10 mg BID, indicating deficits in HRQoL with placebo relative to their normative values.

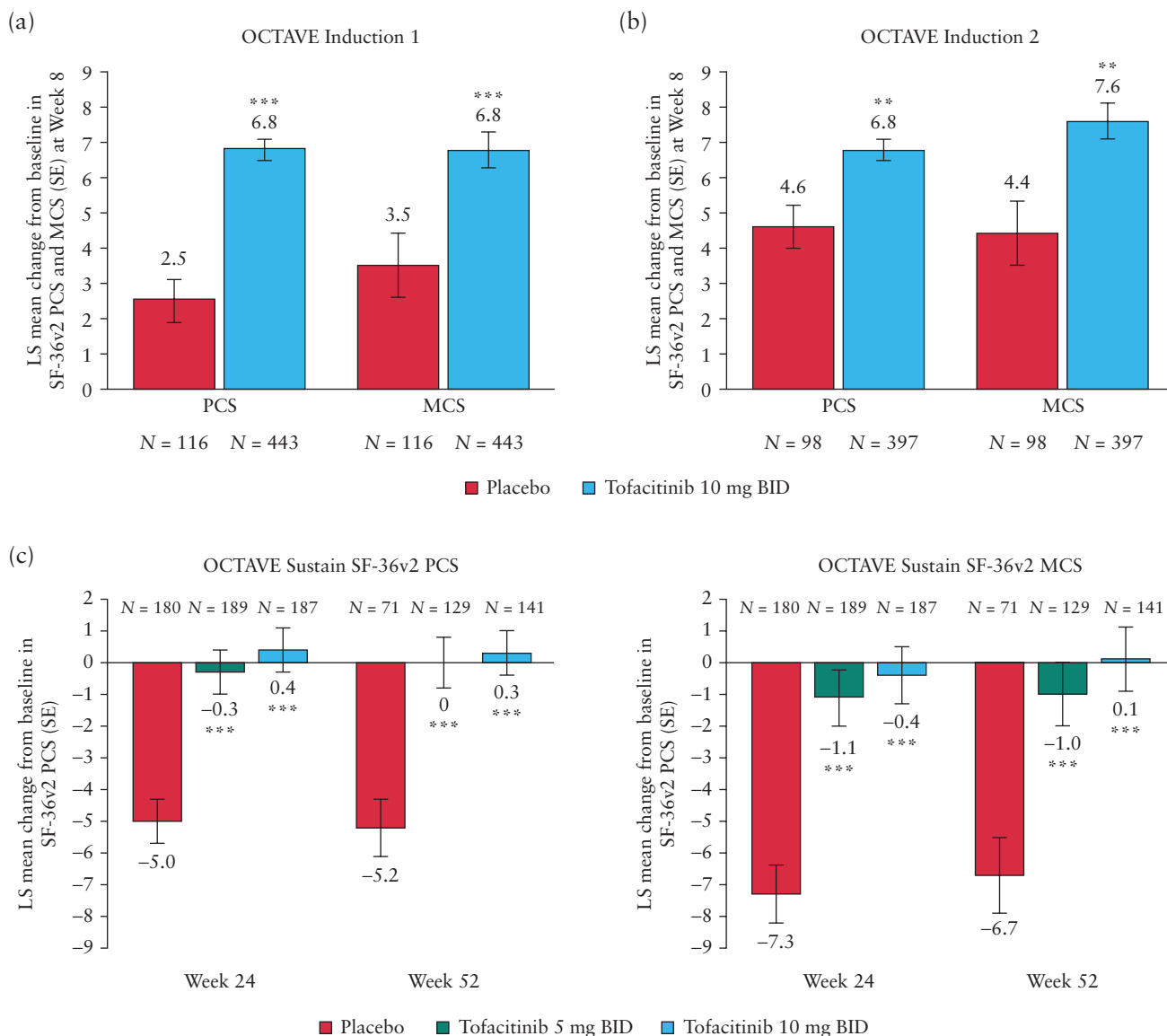


Figure 3. LS mean change from baseline in SF-36v2 PCS and MCS at Week 8 in [A] OCTAVE Induction 1 and [B] OCTAVE Induction 2, and [C] at Weeks 24 and Week 52 in OCTAVE Sustain. BID, twice daily; LME, linear mixed-effects; LS, least squares; MCS, Mental Component Summary; PCS, Physical Component Summary; SE, standard error; SF-36v2, Short Form-36v2® Health Survey. ** $p < 0.01$, *** $p < 0.0001$ versus placebo; data for OCTAVE Induction 1 and 2 are full analysis set, observed case, using analysis of covariance; data for OCTAVE Sustain are full analysis set, observed case, using LME model.

Table 4. LS mean change from baseline in SF-36v2 domain scores over time in OCTAVE Induction 1 and 2.

	OCTAVE Induction 1		OCTAVE Induction 2	
	Placebo [N = 122]	Tofacitinib 10 mg BID [N = 476]	Placebo [N = 112]	Tofacitinib 10 mg BID [N = 429]
LS mean change from baseline in SF-36v2 domain scores at Week 8, mean [SE]				
Physical functioning	2.8 [0.6]	4.7 [0.3]**	3.5 [0.6]	4.9 [0.3]*
Role physical	3.0 [0.8]	8.4 [0.5]***	5.3 [0.9]	8.8 [0.5]**
Bodily pain	3.3 [0.8]	8.7 [0.5]***	6.2 [0.9]	8.7 [0.5]*
General health	2.2 [0.7]	5.6 [0.4]**	3.0 [0.8]	6.2 [0.4]**
Vitality	3.2 [0.9]	8.3 [0.5]***	5.8 [1.0]	8.8 [0.5]**
Social functioning	3.8 [0.9]	8.8 [0.5]***	4.6 [1.0]	9.0 [0.6]**
Role emotional	3.8 [0.9]	6.3 [0.5]*	3.5 [1.1]	6.6 [0.6]**
Mental health	2.9 [0.9]	5.9 [0.5]**	4.9 [1.0]	7.0 [0.5]*

BID, twice daily; LS, least squares; SE, standard error; SF-36v2, Short Form-36v2® Health Survey.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$ versus placebo; data for OCTAVE Induction 1 and 2 are full analysis set, observed case, using analysis of covariance.

Table 5. LS mean change from baseline in SF-36v2 domain scores over time in OCTAVE Sustain.

	OCTAVE Sustain		
	Placebo [N = 198]	Tofacitinib 5 mg BID [N = 198]	Tofacitinib 10 mg BID [N = 197]
LS mean change from baseline in SF-36v2 domain scores, mean [SE]			
Physical functioning			
Week 24	-4.4 [0.7]	-0.5 [0.7]***	0.5 [0.7]***
Week 52	-4.3 [0.8]	-0.7 [0.7]**	0.5 [0.7]***
Role physical			
Week 24	-6.5 [0.8]	-0.5 [0.8]***	0.2 [0.8]***
Week 52	-6.5 [1.1]	0.1 [0.9]***	0.2 [0.9]***
Bodily pain			
Week 24	-7.6 [0.9]	-1.6 [0.9]***	-0.7 [0.9]***
Week 52	-6.9 [1.2]	-0.8 [1.0]***	-0.2 [0.9]***
General health			
Week 24	-4.8 [0.7]	0.7 [0.7]***	0.4 [0.7]***
Week 52	-3.7 [0.9]	1.5 [0.8]***	1.3 [0.7]***
Vitality			
Week 24	-7.6 [0.9]	-1.3 [0.9]***	-0.3 [0.9]***
Week 52	-6.2 [1.2]	-1.0 [1.0]**	-0.7 [1.0]***
Social functioning			
Week 24	-7.4 [0.9]	0.0 [0.9]***	0.5 [0.9]***
Week 52	-7.4 [1.2]	-0.9 [1.0]***	0.7 [1.0]***
Role emotional			
Week 24	-6.1 [0.9]	-0.4 [0.9]***	-0.3 [0.9]***
Week 52	-5.6 [1.2]	0.1 [1.0]***	0.0 [1.0]***
Mental health			
Week 24	-7.7 [0.8]	-1.9 [0.8]***	-0.6 [0.8]***
Week 52	-6.3 [1.1]	-1.2 [0.9]**	0.5 [0.9]***

BID, twice daily; LME, linear mixed-effects; LS, least squares; SE, standard error; SF-36v2, Short Form-36v2® Health Survey.

** $p < 0.01$, *** $p < 0.0001$ versus placebo; data for OCTAVE Sustain are full analysis set, observed case, using LME model.

4. Discussion

In two identically designed Phase 3 studies of tofacitinib induction therapy for patients with moderately to severely active UC, statistically significant and clinically meaningful improvements in HRQoL were observed with tofacitinib 10 mg BID versus placebo, as evidenced by improvement in clinical outcomes and PROs based on the IBDQ and SF-36v2. A significant treatment effect was observed with tofacitinib 10 mg BID versus placebo as early as Week 4 [first post-baseline IBDQ assessment] in the induction studies. In a subsequent Phase 3 maintenance study of tofacitinib, improvements gained by patients during the induction studies were maintained with tofacitinib 5 mg BID and tofacitinib 10 mg BID, but not with placebo. Analyses of HRQoL in subgroups showed a generally consistent effect of treatment regardless of corticosteroid use at baseline, gender, and previous anti-TNF therapy. Patient SF-36v2 scores decreased significantly when treated with placebo in the maintenance study.

These results are consistent with the primary efficacy analyses of OCTAVE Induction 1 and 2, and OCTAVE Sustain,²⁵ where significant improvements in clinical symptoms and endoscopic disease severity were observed with tofacitinib induction therapy and maintained with tofacitinib maintenance therapy.

The importance of assessing HRQoL in clinical trials evaluating new therapies for UC is reflected in draft US Food and Drug Administration guidance to industry.¹⁶ This guidance advises that ideal assessment of efficacy for UC therapies should comprise a PRO assessment of signs and symptoms of disease, complemented by a clinician-reported endoscopic and histological evaluation.¹⁶ In these analyses, we observed significant, but not strong, correlation between

HRQoL endpoints and clinical efficacy in both OCTAVE Induction 1 and 2 and in OCTAVE Sustain. This result is not surprising as the Pearson correlation coefficient, which assumes that two variables follow an underlying continuous [normal] distribution, is expected to attenuate the true relationship between two variables when at least one variable is taken as binary rather than quantitative.^{13,33} A more representative metric to obtain such a true relationship is found using percentages or means, which were reported throughout the manuscript. Moreover, although improvement in clinical measures of disease may correlate with HRQoL at the population level,³⁴ some patients' HRQoL may still be impaired despite achieving clinical goals of therapy such as mucosal healing.³⁵ Accordingly, HRQoL outcomes are important in assessing the effect of UC therapies on how patients feel and their ability to function in daily life.^{21–23} Improvements in HRQoL observed during the OCTAVE Phase 3 programme were consistent with those observed with biological therapies for the treatment of UC—infliximab,¹¹ vedolizumab,³⁶ and adalimumab³⁷—where clinical efficacy was demonstrated along with improvements in HRQoL and functional outcomes.

Generic measures of patients' functioning and well-being, such as the SF-36v2, allow the assessment of whether patients experience improvement in HRQoL, but also whether they become 'well' or normalised: that is, whether their post-treatment scores are comparable to a normal reference group [ie the 1998 US age- and gender-matched normative population]. This approach to assessing treatment benefit is widely adopted in other therapeutic areas, most notably in rheumatology, where a goal of treatment is for the patient to not only feel better but also to achieve levels of functioning and well-being

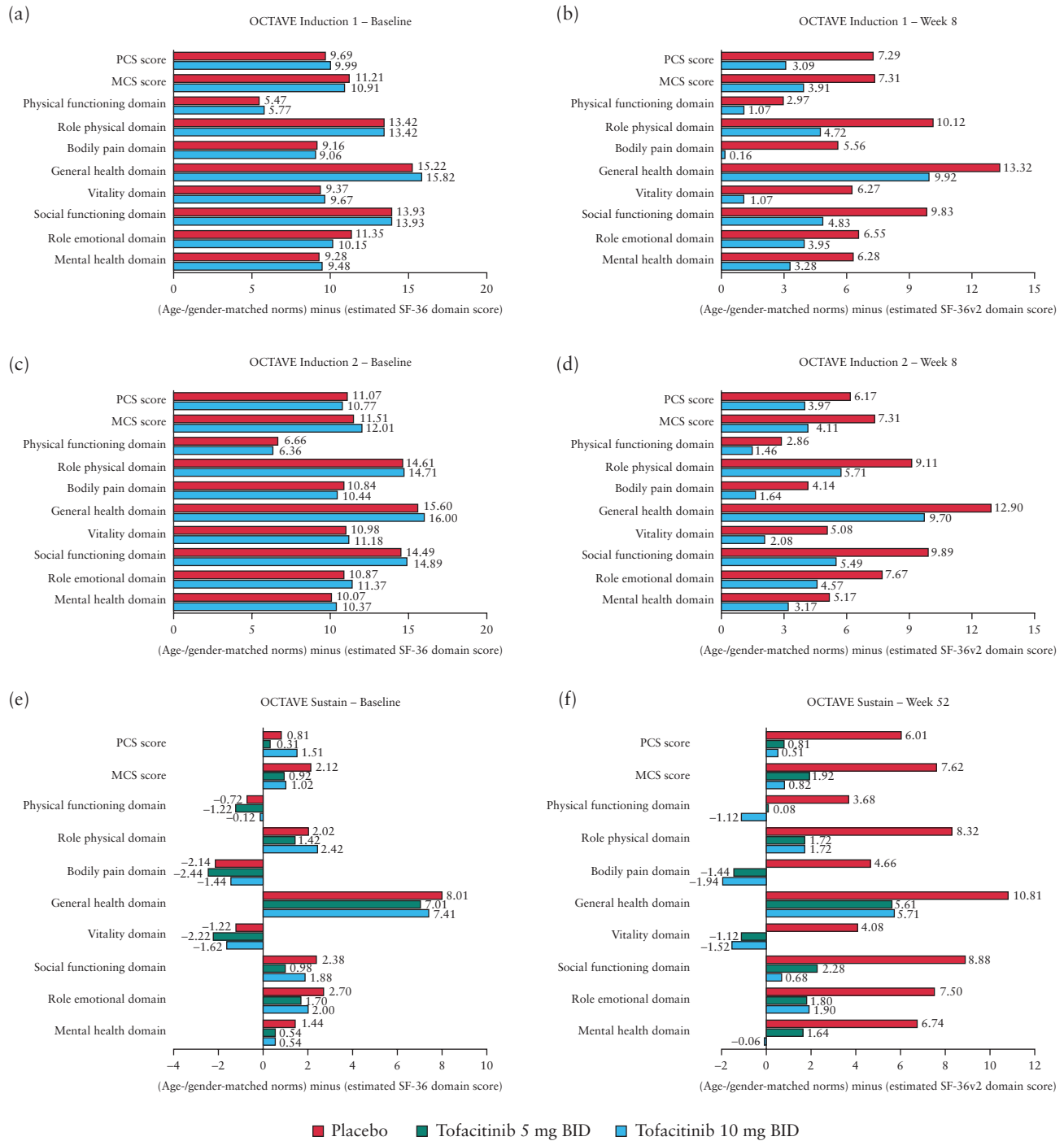


Figure 4. Comparison of SF-36v2 domain, PCS and MCS scores, versus age- and gender-matched norms at baseline [A, C, and E for OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain, respectively] and at Week 8 in [B] OCTAVE Induction 1 and [D] OCTAVE Induction 2, and [F] at Week 52 in OCTAVE Sustain. BID, twice daily; LME, linear mixed-effects; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36v2, Short Form-36v2® Health Survey. Data at baseline are based on descriptive statistics. Week 8 data for OCTAVE Induction 1 and 2 are full analysis set, observed case, using analysis of covariance; Week 52 data for OCTAVE Sustain are full analysis set, observed case, using LME model.

that are measurably ‘normal’ for the patient’s age and gender.³⁸ Mean SF-36v2 PCS and MCS scores at baseline of OCTAVE Induction 1 and OCTAVE Induction 2 ranged from 40.2 to 41.5 and 37.8 to 39.0, respectively, across treatment groups. By comparison, the PCS and MCS scores were 39.0 and 51.9, respectively, for patients with prostate cancer in treatment³⁹; 31.7 and 47.3, respectively, for hospitalised

dialysis patients⁴⁰; and 34.4 and 49.6, respectively, for patients with chronic obstructive pulmonary disease.⁴¹ The *post hoc* analyses performed in these studies demonstrated age- and gender-related induction baseline decrements in HRQoL, as reflected by SF-36v2 data, which were subsequently improved toward normalised status with tofacitinib therapy during the induction studies, but not with placebo.

Furthermore, during OCTAVE Sustain, this normalised status was generally maintained with tofacitinib treatment but not with placebo.

A limitation of these analyses is that the OCTAVE Sustain maintenance study assessed treatment effect in patients who had already demonstrated clinical response in the induction phase. Although this reflects real-life practice, where patients only continue therapy in the case of initial response, further data from the ongoing open-label extension study of tofacitinib in UC [OCTAVE Open; NCT01470612] are required to assess HRQoL improvements in patients who failed to respond to induction treatment. The analyses comparing SF-36v2 scores in OCTAVE Induction 1 and 2 and OCTAVE Sustain versus age- and gender-matched norms were not prespecified analyses, and should be interpreted cautiously. In addition, during OCTAVE Sustain, a greater proportion of patients in the placebo group discontinued the study compared with patients receiving tofacitinib 5 mg BID and 10 mg BID. This should be taken into account when interpreting the efficacy analyses based on observed case data.

In conclusion, induction therapy with tofacitinib 10 mg BID significantly improved HRQoL as early as 4 weeks in patients with moderately to severely active UC. In patients with clinical response in the induction studies, improvements in HRQoL gained during the induction studies were maintained with tofacitinib 5 mg BID and tofacitinib 10 mg BID and were significantly better than with placebo throughout 52 weeks of maintenance therapy.

Funding

This work was supported by Pfizer Inc. Medical writing support was funded by Pfizer Inc.

Conflict of Interest

JP has received: consulting fees from AbbVie, Boehringer Ingelheim, Celgene, Ferring, Genentech-Roche, Janssen, MSD, Pfizer Inc, Second Genome, Shire, Takeda, Theravance, TiGenix, and Topivert; research grants from AbbVie and MSD; and speaker fees from AbbVie, Biogen, Janssen, MSD, and Pfizer Inc. SV has received: consulting fees from Takeda, Roche/Genentech, Merck, Centocor, AbbVie, UCB, Pfizer Inc, Ferring, Second Genome, and Galapagos; research grants from Centocor, AbbVie, Takeda, Pfizer Inc, and Merck; and lecture and/or speaker bureau fees from Merck, AbbVie, Takeda, Pfizer Inc, Ferring, Falk, and Centocor. JOL has received: consulting fees from AbbVie, Celgene, Ferring, Janssen, Merck, Robarts Clinical Trials, Shire, Pfizer Inc, and Takeda; research grants from MSD, Hospira [Pfizer Inc], Shire, and Takeda; lecture and/or speaker bureau fees from AbbVie, Allergan, Ferring, Janssen, MSD, Shire, and Takeda; and advisory board fees from AbbVie, Atlantic Healthcare, Ferring, Hospira [Pfizer Inc], Janssen, MSD, NAP, Shire, Pfizer Inc, Takeda, and Vifor. BES has received: consulting fees from AbbVie, Akros Pharma, Amgen, AstraZeneca, Boehringer Ingelheim, Celgene, Forest Research Institute, Lilly, MedImmune, Puretech Ventures, LLC, Receptos, Salix, Shire, Takeda, Topivert Pharma, Vedanta Biosciences, Bristol-Myers Squibb, Janssen R&D, Luitpold Pharmaceuticals, Pfizer Inc, Prometheus Laboratories, Synergy Pharmaceuticals, Takeda, Theravance Biopharma, and Tigenix; and research grants from AbbVie, Celgene, GlaxoSmithKline, Janssen R&D, Pfizer Inc, Prometheus Laboratories, and Takeda. CS, GF, HZ, JCC, and AGB are employees and stockholders of Pfizer Inc. AY, MB, and SM are employees of Optum and were paid consultants to Pfizer Inc in connection with the development of this manuscript. DTR has received: consulting fees from AbbVie, Amgen, Janssen, Pfizer Inc, Takeda, and UCB; and research grants from AbbVie, Genentech, Janssen, Takeda, and UCB.

Acknowledgments

The authors would like to thank the patients and their families, the investigators and the study teams who were involved in OCTAVE Induction 1, OCTAVE

Induction 2, and OCTAVE Sustain, Paul Healey [an employee of Pfizer Inc at the time these analyses were conducted], Cem Kayhan of Pfizer Inc, and Alireza Manuchehri of Pfizer Ltd for their contributions to the preparation of this manuscript. These studies were sponsored by Pfizer Inc. Medical writing support under the guidance of the authors was provided by Daniel Binks PhD at Complete Medical Communications, Macclesfield, UK and was funded by Pfizer Inc, New York, NY, USA in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015;163:461–4).

Author Contributions

The study concept and design were developed by JP, SV, JOL, BES, and DTR in collaboration with the sponsor, Pfizer Inc. JP, SV, JOL, BES, and DTR were involved in recruitment of study patients. All authors were involved in the analysis and/or interpretation of the data, and were involved in drafting the manuscript and critically evaluating it for important intellectual content. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012;380:1606–19.
2. Waljee AK, Joyce JC, Wren PA, Khan TM, Higgins PD. Patient reported symptoms during an ulcerative colitis flare: a Qualitative Focus Group Study. *Eur J Gastroenterol Hepatol* 2009;21:558–64.
3. Wolfe BJ, Sirois FM. Beyond standard quality of life measures: the subjective experiences of living with inflammatory bowel disease. *Qual Life Res* 2008;17:877–86.
4. Devlen J, Beusterien K, Yen L, Ahmed A, Cheifetz AS, Moss AC. Barriers to mesalamine adherence in patients with inflammatory bowel disease: a qualitative analysis. *J Manag Care Spec Pharm* 2014;20:309–14.
5. Sammut J, Scerri J, Xuereb RB. The lived experience of adults with ulcerative colitis. *J Clin Nurs* 2015;24:2659–67.
6. Jansen F, van Uden-Kraan CF, Braakman JA, van Keizerswaard PM, Witte BI, Verdonck-de Leeuw IM. A mixed-method study on the generic and ostomy-specific quality of life of cancer and non-cancer ostomy patients. *Support Care Cancer* 2015;23:1689–97.
7. McCormick JB, Hammer RR, Farrell RM, et al. Experiences of patients with chronic gastrointestinal conditions: in their own words. *Health Qual Life Outcomes* 2012;10:25.
8. Hughes LD, King L, Morgan M, et al. Food-related quality of life in inflammatory bowel disease: development and validation of a questionnaire. *J Crohns Colitis* 2016;10:194–201.
9. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations [EFCCA] patient survey. *J Crohns Colitis* 2007;1:10–20.
10. Reinisch W, Sandborn WJ, Bala M, et al. Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis. *Inflamm Bowel Dis* 2007;13:1135–40.
11. Feagan BG, Reinisch W, Rutgeerts P, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. *Am J Gastroenterol* 2007;102:794–802.
12. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014;146:392–400.e3.
13. Panés J, Su C, Bushmakin AG, Cappelleri JC, Mamolo C, Healey P. Randomised trial of tofacitinib in active ulcerative colitis: analysis of efficacy based on patient-reported outcomes. *BMC Gastroenterol* 2015;15:14.

14. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007;132:763–86.
15. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2014;12:1246–56.e6.
16. Food and Drug Administration. *Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry*. 2016. <http://www.fda.gov/downloads/Drugs/Guidances/UCM515143.pdf> Accessed March 28, 2017.
17. Cappelleri JC, Zou KH, Bushmakina AG, Alvir JM, Alemayehu D, Symonds T. *Patient-Reported Outcomes: Measurement, Implementation and Interpretation*. Boca Raton, FL: Chapman & Hall/CRC; 2013.
18. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353–65.
19. Rubin DT, Siegel CA, Kane SV, et al. Impact of ulcerative colitis from patients' and physicians' perspectives: Results from the UC: NORMAL survey. *Inflamm Bowel Dis* 2009;15:581–8.
20. Schreiber S, Panés J, Louis E, Holley D, Buch M, Paridaens K. Perception gaps between patients with ulcerative colitis and healthcare professionals: an online survey. *BMC Gastroenterol* 2012;12:108.
21. US Dept of Health, FDA, CDER, CBER, CDRH. *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. 2009. <https://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf> Accessed March 29, 2017.
22. European Medicines Agency. *Reflection Paper on the Use of Patient Reported Outcome [PRO] Measures in Oncology Studies*. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500168852.pdf Accessed March 28, 2017.
23. Medical Research Council. *Patient-Reported Outcome Measures [PROMs]: Identifying UK Research Priorities*. 2009. <https://www.mrc.ac.uk/documents/pdf/patient-reported-outcome-measures-proms-identifying-uk-research-priorities1/> Accessed March 28, 2017.
24. Sandborn WJ, Ghosh S, Panes J, et al.; Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012;367:616–24.
25. Sandborn WJ, Su C, Sands BE, et al.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;376:1723–36.
26. Guyatt GH, Deyo RA, Charlson M, Levine MN, Mitchell A. Responsiveness and validity in health status measurement: a clarification. *J Clin Epidemiol* 1989;42:403–8.
27. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology* 1994;106:287–96.
28. Pallis AG, Mouzas IA, Vlachonikolis IG. The inflammatory bowel disease questionnaire: a review of its national validation studies. *Inflamm Bowel Dis* 2004;10:261–9.
29. Maruish ME, editor. *User's Manual for the SF-36v2® Health Survey*. 3rd edn. Lincoln, RI: QualityMetric Inc; 2011.
30. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989;96:804–10.
31. Van Belle G, Fisher LD, Heagerty PJ, Lumley T. *Biostatistics: A Methodology for the Health Sciences*. 2nd edn. New York, NY: John Wiley & Sons; 2004.
32. Ware JE Jr. *User's Manual for the Sf-36v2 Health Survey*. 2nd edn. London: Quality Metric; 2007.
33. Nunnally JC, Bernstein IH. *Psychometric Theory*. 3rd edn. New York, NY: McGraw-Hill; 1994.
34. Kalafateli M, Triantos C, Theocharis G, et al. Health-related quality of life in patients with inflammatory bowel disease: a single-center experience. *Ann Gastroenterol* 2013;26:243–8.
35. Casellas F, Barreiro de Acosta M, Iglesias M, et al. Mucosal healing restores normal health and quality of life in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2012;24:762–9.
36. Feagan BG, Patel H, Colombel JF, et al. Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial. *Aliment Pharmacol Ther* 2017;45:264–75.
37. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012;142:257–65.e1–3.
38. Strand V, Boers M, Idzerda L, et al. It's good to feel better but it's better to feel good and even better to feel good as soon as possible for as long as possible. Response criteria and the importance of change at OMERACT 10. *J Rheumatol* 2011;38:1720–7.
39. Baker F, Haffer SC, Denniston M. Health-related quality of life of cancer and noncancer patients in Medicare managed care. *Cancer* 2003;97:674–81.
40. Lacson E Jr, Xu J, Lin SF, Dean SG, Lazarus JM, Hakim RM. A comparison of SF-36 and SF-12 composite scores and subsequent hospitalization and mortality risks in long-term dialysis patients. *Clin J Am Soc Nephrol* 2010;5:252–60.
41. Pickard AS, Yang Y, Lee TA. Comparison of health-related quality of life measures in chronic obstructive pulmonary disease. *Health Qual Life Outcomes* 2011;9:26.