

Tofacitinib in Patients with Ulcerative Colitis: Inflammatory Bowel Disease Questionnaire Items in Phase 3 Randomized Controlled Induction Studies

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Background: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). We examined the effect of tofacitinib induction treatment on Inflammatory Bowel Disease Questionnaire (IBDQ) items in adults with moderate to severe UC.

Methods: Data were pooled from the randomized, 8-week, double-blind, phase 3 OCTAVE Induction 1 and 2 studies. The IBDQ was self-administered by patients at baseline, week 4, and week 8, with higher scores indicating better health-related quality of life (HRQoL). Change from baseline in IBDQ items was analyzed for 10 mg of tofacitinib twice daily (BID) vs placebo using a linear mixed-effects model, with no multiplicity adjustment performed. Effect sizes were calculated. Subgroup analyses by tumor necrosis factor inhibitor (TNFi) experience were performed.

Results: Significant improvements (nominal $P < 0.05$) were observed in all IBDQ items with 10 mg of tofacitinib BID vs placebo at weeks 4 and 8. For the overall population, the largest treatment differences across all items were reported for “bowel movements been loose” at weeks 4 and 8, and “problem with rectal bleeding” at week 8 (mean treatment differences all 1.1; both in bowel symptoms domain). These items also showed the largest effect sizes. Treatment benefits were generally slightly numerically higher in TNFi-experienced vs TNFi-naïve patients.

Conclusions: Tofacitinib induction therapy improved all IBDQ items vs placebo in patients with UC, reflecting improvements in HRQoL, with greatest benefits reported in bowel symptoms domain items (Funded by Pfizer Inc; OCTAVE Induction 1 and OCTAVE Induction 2; ClinicalTrials.gov, NCT01465763 and NCT01458951, respectively).

Key Words: ulcerative colitis, tofacitinib, patient-reported outcomes

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the mucosa of the colon, with rectal bleeding and diarrhea the most common symptoms observed. In addition, patients can suffer from urgency, abdominal pain, incontinence, mucous discharge, night-time bowel movements, fatigue, fever, and weight loss.¹

In addition to these bowel-related and systemic symptoms, patients with UC also report effects on their emotional functioning, including anxiety, depression, and fear, and their social functioning.²⁻⁵ Patients have reported anxiety relating to their UC symptoms controlling their lives, which consequently affects their health-related quality of life (HRQoL).² Furthermore, a strong association among disease activity, disease-specific HRQoL, and psychological functioning has

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been shown in patients with UC.⁶ Therefore, UC therapies that improve clinical outcomes can also result in improvements in HRQoL measures.^{7,8}

Different instruments have been developed for the assessment of HRQoL in patients with inflammatory bowel disease (IBD), with the Inflammatory Bowel Disease Questionnaire (IBDQ) identified as the most widely used instrument with good reliability and validity.⁹ The IBDQ comprises 32 individual items that are grouped into 4 domains: bowel symptoms, systemic symptoms, emotional function, and social function.^{10,11} However, the IBDQ is time-consuming to utilize; consequently, it is not routinely used in clinical practice.¹²

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of UC. The efficacy and safety of tofacitinib has previously been shown in a phase 2 study, two phase 3 induction studies (OCTAVE Induction 1 and 2), a phase 3 maintenance study (OCTAVE Sustain), and an ongoing phase 3, open-label, long-term extension study.¹³⁻¹⁵ Furthermore, a previous publication has reported the findings for IBDQ total and domain scores for patients in the tofacitinib OCTAVE Induction 1 and 2 and OCTAVE Sustain phase 3 studies, with significant improvements reported with 10 mg of tofacitinib twice daily (BID) vs placebo in all 4 IBDQ domains at week 4 and week 8 in OCTAVE Induction 1 and 2 and with 5 and 10 mg of tofacitinib BID vs placebo in all 4 IBDQ domains at week 8, week 24, and week 52 in OCTAVE Sustain.¹⁶ However, this publication did not analyze the effect of tofacitinib on the individual IBDQ items within each domain.

The objective of the current analyses was to enrich understanding of the treatment effect of 10 mg of tofacitinib BID vs placebo on individual items of the IBDQ at weeks 4 and 8 by using data from the OCTAVE Induction 1 and 2 studies. To our knowledge, this is the first evaluation of the effect of any UC therapy on each individual IBDQ item.

MATERIALS AND METHODS

Study Design

OCTAVE Induction 1 and 2 (NCT01465763 and NCT01458951) were identical 8-week, double-blind, placebo-controlled, multicenter, phase 3 induction studies in which patients were randomized 1:4 to receive placebo or 10 mg of tofacitinib BID (Fig. 1).¹⁴ There was a small number of patients who received 15 mg of tofacitinib BID before a protocol amendment who were excluded from these analyses.

Patients

Inclusion and exclusion criteria have been described previously.¹⁴ Briefly, patients (18 years and older) were required to have moderately to severely active disease (Mayo score 6–12, with a rectal bleeding subscore 1–3, and an endoscopic subscore of 2 or 3) and a confirmed UC diagnosis for at least 4 months.

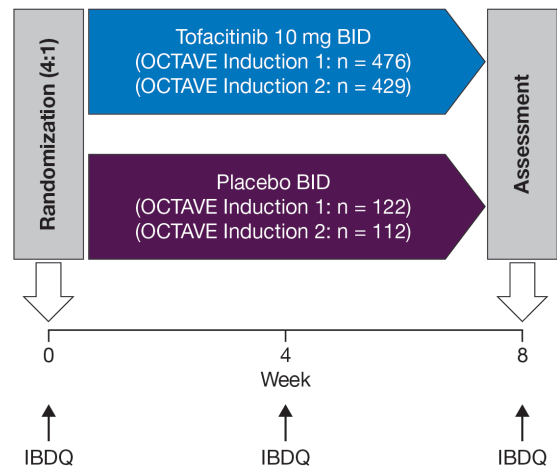


FIGURE 1. Study design of OCTAVE Induction 1 and 2. Final complete efficacy assessment at week 8. Treatment continued up to week 9; n, number of patients randomized in each treatment group.

Treatment failure or intolerance to oral or intravenous glucocorticoids, azathioprine, mercaptopurine, infliximab, and/or adalimumab was a requirement for study entry. Exclusion criteria included clinical findings suggestive of Crohn's disease, UC limited to the distal 15 cm of the colon, clinical signs of fulminant colitis, toxic megacolon, or indeterminate, microscopic, ischemic, or infectious colitis.

Concomitant oral 5-aminosalicylates and oral corticosteroids (at a maximum dose of 25 mg per day of prednisone or a prednisone equivalent) were permitted, provided that the dose remained stable throughout the induction studies, with a mandatory steroid tapering schedule to commence upon entry into the maintenance study. Tumor necrosis factor inhibitors (TNFi) were prohibited, with a washout period of 8 weeks required. Azathioprine, methotrexate, and 6-mercaptopurine were also prohibited, with a washout period of 2 weeks required.

Inflammatory Bowel Disease Questionnaire

The IBDQ consists of 4 domains and 32 items. Items are rated on a 7-point scale, with 7 representing best function and 1 representing worst function, providing a total score ranging from 32 to 224; therefore, higher scores indicate better HRQoL.¹¹ The bowel symptom domain consists of 10 items (total domain score range 10–70), the systemic symptom domain consists of 5 items (total domain score range 5–35), the emotional function domain consists of 12 items (total domain score range 12–84), and the social function domain consists of 5 items (total domain score range 5–35).¹¹ The 32 IBDQ questions pertaining to each item are detailed in [Supplementary Table 1](#). In OCTAVE Induction 1 and 2, the IBDQ was self-administered by patients at baseline, week 4, and week 8.

Statistical Analyses

Baseline demographics, baseline clinical characteristics, and IBDQ item scores at baseline, week 4, and week 8 were summarized descriptively.¹⁷

The change from baseline in IBDQ item scores at week 4 and week 8 were analyzed for 10 mg of tofacitinib BID vs placebo using the same linear mixed-effects (longitudinal) model,¹⁸ as previously used for the overall and domain IBDQ scores.¹⁶ Missing data were handled by the linear-mixed effects model and were not imputed otherwise. Treatment, study, prior treatment with TNFi, corticosteroid use at baseline, geographic region, week (categorical covariate), treatment-by-week interaction, and baseline score were fixed effects in the model, and patient was a random effect. Treatment comparisons at each time point were made within this model. This was an ad hoc analysis for exploratory purposes only. No adjustment was performed for multiplicity, with nominal *P* values reported.

Standardized effect sizes for each IBDQ item (to quantify the size of the difference between 10 mg of tofacitinib BID and placebo) were calculated as the difference in least squares means (LSMs) for 10 mg of tofacitinib BID vs placebo, divided by the standard deviation (SD) of baseline scores, where the SD was calculated using data from both treatment groups for all patients in both studies. Based initially on (standardized) effect sizes where 0.1 = trivial, 0.2 = small, 0.5 = medium, and 0.8 = large,^{19,20} the midpoints between each of these values were used to create categorization intervals on effect size as adjectival descriptors across its entire possible range (in absolute value): 0 to 0.15, trivial; >0.15 to 0.35, small; >0.35 to 0.65, medium; and >0.65, large.

Analyses were performed overall by pooling data from the 2 studies. In addition, subgroup analyses were performed in TNFi-naïve and TNFi-experienced patients.

ETHICAL CONSIDERATIONS

Both 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 (IRBs) and/or independent ethics committees at each of the investigational centers participating in the studies or a central IRB. All patients provided written informed consent.

RESULTS

Patients

In the pooled OCTAVE Induction 1 and 2 studies, 234 patients were randomized to receive placebo, and 905 patients were randomized to receive 10 mg of tofacitinib BID. Overall, the majority of patients (age, mean [SD] 41.2 [13.9] years) were male (58.6%), white (80.1%), had never smoked (64.1%), had extensive/pancolitis UC (51.5%), and had received prior

TNFi (54.3%), corticosteroid (90.3%), or immunosuppressant (74.0%) treatment. Baseline demographics and disease characteristics were generally similar between treatment arms for all patients, TNFi-naïve patients, and TNFi-experienced patients. Some numerical differences were observed when comparing patients with and without prior TNFi experience, including a numerically higher proportion of TNFi-experienced patients having extensive/pancolitis disease extent and previously receiving and failing immunosuppressant treatment compared with TNFi-naïve patients (Table 1).

Baseline Distribution of IBDQ Items

In the overall population in the pooled Induction 1 and 2 studies, the IBDQ items within each domain that had the lowest baseline scores and were impacted the most by disease were “bowel movements been loose” and “problem with rectal bleeding” (mean 2.3 in both treatment arms) for the bowel symptom domain; “getting good night’s sleep” (mean 3.1 and 3.0 for 10 mg of tofacitinib BID and placebo, respectively) for the systemic symptom domain; “felt relaxed/free of tension” (mean 2.9 and 2.8 for 10 mg of tofacitinib BID and placebo, respectively) for the emotional function domain; “difficulty doing leisure/sports” (mean 3.1 and 3.0 for 10 mg of tofacitinib BID and placebo, respectively) for the social function domain. The baseline distribution for each IBDQ item was generally similar between the 2 treatment groups. Furthermore, baseline IBDQ item scores were generally similar between the overall population and TNFi-naïve and TNFi-experienced patients (Table 2).

Change from Baseline in IBDQ Items

In the overall population in the pooled Induction 1 and 2 studies, significant differences (nominal *P* value < 0.05) in the changes from baseline for 10 mg of tofacitinib BID vs placebo were observed in all IBDQ items at week 4 and week 8. Within each domain, the largest numerical differences for 10 mg of tofacitinib BID vs placebo in the overall population were reported for “bowel movements been loose” at week 4 (difference 1.1; 95% confidence interval [CI], 0.8–1.3) and week 8 (difference 1.1; 95% CI, 0.9–1.4; both *P* < 0.0001), and “problem with rectal bleeding” at week 8 (difference 1.1; 95% CI, 0.9–1.4; *P* < 0.0001) for the bowel symptoms domain. These were also reported for “getting a good night’s sleep” at week 4 (difference 0.8; 95% CI, 0.6–1.0) and week 8 (difference 0.9; 95% CI, 0.7–1.1; both *P* < 0.0001) for the systemic symptoms domain. They were also reported for “fear of not finding a washroom” at week 4 (difference 0.6; 95% CI, 0.3–0.8) and week 8 (difference 0.8; 95% CI, 0.6–1.0; both *P* < 0.0001), “felt embarrassed” at week 4 (difference 0.6; 95% CI, 0.4–0.9; *P* < 0.0001), and “felt angry” at week 4 (difference 0.6; 95% CI, 0.4–0.8; *P* < 0.0001) for the emotional function domain; They were also reported for “avoid attending events” at week 4 (difference 0.8; 95% CI, 0.5–1.0) and week 8 (difference 1.0; 95%

TABLE 1. Demographics and Baseline Disease Characteristics for Patients in the Pooled OCTAVE Induction 1 and 2 Studies (FAS)

	All Patients			TNFi-naïve Patients			TNFi-experienced Patients		
	Placebo	Tofacitinib	Overall	Placebo	Tofacitinib	Overall	Placebo	Tofacitinib	Overall
	(N = 234)	10 mg BID (N = 905)	(N = 1139)	(N = 104)	10 mg BID (N = 417)	(N = 521)	(N = 130)	10 mg BID (N = 488)	(N = 618)
Age (years), mean (SD)	41.1 (14.4)	41.2 (13.8)	41.2 (13.9)	43.2 (13.9)	41.1 (13.5)	41.5 (13.6)	39.4 (14.5)	41.3 (14.1)	40.9 (14.2)
Male, n (%)	132 (56.4)	536 (59.2)	668 (58.6)	64 (61.5)	249 (59.7)	313 (60.1)	68 (52.3)	287 (58.8)	355 (57.4)
White, n (%)	186 (79.5)	726 (80.2)	912 (80.1)	83 (79.8)	335 (80.3)	418 (80.2)	103 (79.2)	391 (80.1)	494 (79.9)
Never smoked, n (%)	161 (68.8)	569 (62.9)	730 (64.1)	75 (72.1)	282 (67.6)	357 (68.5)	86 (66.2)	287 (58.8)	373 (60.4)
Body mass index (kg/m ²), ^a mean (SD)	24.6 (4.7)	24.9 (5.0)	24.8 (4.9)	24.9 (4.3)	25.2 (5.2)	25.2 (5.0)	24.4 (5.0)	24.6 (4.8)	24.6 (4.9)
Disease extent, ^b n (%)									
Proctosigmoiditis	35 (15.0)	132 (14.6)	167 (14.7)	23 (22.3)	69 (16.6)	92 (17.7)	12 (9.2)	63 (12.9)	75 (12.2)
Left-sided colitis	76 (32.6)	307 (34.0)	383 (33.7)	35 (34.0)	160 (38.5)	195 (37.6)	41 (31.5)	147 (30.2)	188 (30.5)
Extensive/ pancolitis	122 (52.4)	463 (51.3)	585 (51.5)	45 (43.7)	186 (44.7)	231 (44.5)	77 (59.2)	277 (56.9)	354 (57.4)
Proctitis	0 (0.0)	1 (0.1) _c	1 (0.1)	0 (0.0)	1 (0.2) _c	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Extraintestinal manifestations present, ^d n (%)	58 (24.9)	249 (27.6)	307 (27.0)	15 (14.6)	101 (24.3)	116 (22.4)	43 (33.1)	148 (30.4)	191 (31.0)
Mayo score, ^e mean (SD)	9.0 (1.5)	9.0 (1.4)	9.0 (1.4)	8.8 (1.4)	8.8 (1.4)	8.8 (1.4)	9.1 (1.5)	9.1 (1.4)	9.1 (1.4)
Prior TNFi treatment, n (%)	130 (55.6)	488 (53.9)	618 (54.3)	0 (0.0)	0 (0.0)	0 (0.0)	130 (100.0)	488 (100.0)	618 (100.0)
Prior corticosteroid treatment, n (%)	217 (92.7)	812 (89.7)	1029 (90.3)	101 (97.1)	375 (89.9)	476 (91.4)	116 (89.2)	437 (89.5)	553 (89.5)
Oral corticosteroid use at baseline, n (%)									
<15 mg/day _f	35 (34.3)	122 (32.4)	157 (32.8)	14 (33.3)	49 (29.3)	63 (30.1)	21 (35.0)	73 (34.9)	94 (34.9)
≥15 mg/day _f	67 (65.7)	254 (67.6)	321 (67.2)	28 (66.7)	118 (70.7)	146 (69.9)	39 (65.0)	136 (65.1)	175 (65.1)
Prior immunosuppressant treatment, n (%)	160 (68.4)	683 (75.5)	843 (74.0)	57 (54.8)	266 (63.8)	323 (62.0)	103 (79.2)	417 (85.5)	520 (84.1)
Prior immunosuppressant failure, n (%)	158 (67.5)	661 (73.0)	819 (71.9)	57 (54.8)	263 (63.1)	320 (61.4)	101 (77.7)	398 (81.6)	499 (80.7)

*All patients: placebo, N = 233; 10 mg of tofacitinib BID, N = 905; TNFi-naïve patients: placebo, N = 104; 10 mg of tofacitinib BID, N = 417; TNFi-experienced patients: placebo, N = 129; 10 mg of tofacitinib BID, N = 488; ^bAll patients: placebo, N = 233; 10 mg of tofacitinib BID, N = 903; TNFi-naïve patients: placebo, N = 103; 10 mg of tofacitinib BID, N = 416; TNFi-experienced patients: placebo, N = 130; 10 mg of tofacitinib BID, N = 487; ^cOne patient with proctitis was enrolled as a protocol deviation; ^dAll patients: placebo, N = 233; 10 mg of tofacitinib BID, N = 902; TNFi-naïve patients: placebo, N = 103; 10 mg of tofacitinib BID, N = 415; TNFi-experienced patients: placebo, N = 130; 10 mg of tofacitinib BID, N = 487; ^eAll patients: placebo, N = 233; 10 mg of tofacitinib BID, N = 903; TNFi-naïve patients: placebo, N = 104; 10 mg of tofacitinib BID, N = 417; TNFi-experienced patients: placebo, N = 129; 10 mg of tofacitinib BID, N = 486; ^fAll patients: placebo, N = 102; 10 mg of tofacitinib BID, N = 376; TNFi-naïve patients: placebo, N = 42; 10 mg of tofacitinib BID, N = 167; TNFi experienced patients: placebo, N = 60; 10 mg of tofacitinib BID, N = 209; excludes patients who took budesonide or beclomethasone.

Abbreviation: FAS, full analysis set.

CI, 0.7–1.2; both $P < 0.0001$) and “difficulty doing leisure/sports” at week 8 (difference 1.0; 95% CI, 0.8–1.2; $P < 0.0001$) for the social function domain (Table 3).

Furthermore, treatment benefits were numerically higher in TNFi-experienced patients vs TNFi-naïve patients in many IBDQ items, with differences more marked in some IBDQ items including “bowel movement frequency,” “getting a good night’s sleep,” “fear of not finding a washroom,” and “difficulty doing leisure/sports” (Supplementary Tables 2 and 3).

Effect Sizes of IBDQ Items

For the overall population, large effect sizes (>0.65) were observed for 2 IBDQ items: “bowel movements been loose” and “problem with rectal bleeding” at weeks 4 and 8 (both within the bowel symptom domain). Small or medium effect sizes (>0.15 – 0.65) were observed for all other IBDQ items, with the exception of “problem with maintaining weight” (systemic symptom domain) and “lack of understanding from others” (emotional function domain) at weeks 4 and 8, both of which had trivial effect sizes (0–0.15; Fig. 2A–D).

TABLE 2. Mean Baseline Distribution of Each IBDQ Item in the Overall Population and by TNFi Experience (FAS, Observed Case)

Mean (SD)	Overall Population		TNFi-naïve		TNFi-experienced	
	Placebo (N = 234)	Tofacitinib 10 mg BID (N = 905)	Placebo (N = 104)	Tofacitinib 10 mg BID (N = 417)	Placebo (N = 130)	Tofacitinib 10 mg BID (N = 488)
Bowel symptoms						
1. Bowel movement frequency	3.4 (1.6) _a	3.4 (1.6) _b	3.4 (1.5) _c	3.4 (1.5) _d	3.5 (1.7)	3.4 (1.7) _e
5. Bowel movements been loose	2.3 (1.4)	2.3 (1.3) _f	2.3 (1.5)	2.3 (1.3) _g	2.2 (1.4)	2.3 (1.3) _h
9. Troubled by cramps	3.8 (1.5)	3.9 (1.7) _f	3.8 (1.5)	3.9 (1.6) _g	3.8 (1.6)	3.9 (1.7) _h
13. Troubled by pain	3.8 (1.5)	3.9 (1.6) _f	3.8 (1.4)	4.0 (1.6) _g	3.8 (1.6)	3.9 (1.6) _h
17. Problems with passing gas	3.9 (1.6)	3.8 (1.7) _f	3.9 (1.5)	3.8 (1.7) _g	3.9 (1.7)	3.9 (1.7) _h
20. Troubled by bloating	3.9 (1.6)	3.9 (1.6) _f	4.0 (1.5)	3.8 (1.6) _g	3.9 (1.6)	4.0 (1.7) _h
22. Problem with rectal bleeding	2.3 (1.3)	2.3 (1.3) _i	2.3 (1.3)	2.3 (1.4) _g	2.2 (1.3)	2.4 (1.3) _j
24. Feeling of having to go	3.6 (1.5)	3.5 (1.4) _i	3.4 (1.4)	3.4 (1.4) _g	3.7 (1.5)	3.6 (1.4) _j
26. Accidental soiling underpants	4.9 (1.7)	4.7 (1.6) _k	4.8 (1.7)	4.8 (1.7) _l	5.0 (1.6)	4.6 (1.6) _m
29. Troubled by nausea	5.2 (1.6)	5.2 (1.6) _f	5.3 (1.7)	5.2 (1.6) _g	5.1 (1.6)	5.2 (1.5) _h
Systemic symptoms						
2. Feeling fatigued or tired	3.2 (1.4)	3.2 (1.4) _f	3.2 (1.5)	3.2 (1.4) _g	3.2 (1.3)	3.2 (1.4) _h
6. How much energy have you had	3.4 (1.2)	3.4 (1.3) _f	3.4 (1.2)	3.4 (1.3) _g	3.4 (1.2)	3.5 (1.2) _h
10. Felt generally unwell	3.4 (1.5)	3.5 (1.5) _i	3.3 (1.5)	3.5 (1.5) _g	3.4 (1.5)	3.5 (1.6) _j
14. Getting good night's sleep	3.0 (1.7)	3.1 (1.7) _f	3.1 (1.6)	3.3 (1.8) _g	2.9 (1.8)	2.9 (1.6) _h
18. Problem maintaining weight	4.6 (1.9) _n	4.5 (2.0) _i	4.6 (2.0)	4.4 (2.0) _g	4.6 (1.9) _o	4.6 (2.0) _j
Emotional function						
3. Felt frustrated/impatient/restless	3.8 (1.5)	3.9 (1.5) _f	3.7 (1.5)	3.8 (1.5) _g	4.0 (1.6)	4.0 (1.5) _h
7. Worry about needing surgery	4.7 (1.8)	4.7 (1.8) _f	4.8 (1.9)	4.7 (1.8) _g	4.6 (1.8)	4.6 (1.7) _h
11. Fear of not finding a washroom	3.2 (1.7)	3.3 (1.7) _f	3.2 (1.7)	3.5 (1.7) _g	3.2 (1.7)	3.2 (1.7) _h
15. Felt depressed/discouraged	4.1 (1.6)	4.2 (1.6) _f	3.9 (1.6)	4.1 (1.6) _g	4.3 (1.6)	4.2 (1.6) _h
19. Felt worried or anxious	3.8 (1.7)	3.7 (1.6) _f	3.4 (1.6)	3.7 (1.7) _g	4.1 (1.7)	3.7 (1.6) _h
21. Felt relaxed/free of tension	2.8 (1.2)	2.9 (1.3) _i	2.7 (1.1)	2.7 (1.3) _g	2.9 (1.2)	3.0 (1.3) _j
23. Felt embarrassed	3.7 (1.8)	3.7 (1.7) _i	3.7 (1.8)	3.6 (1.7) _g	3.7 (1.7)	3.8 (1.6) _j
25. Felt tearful or upset	4.8 (1.6)	4.8 (1.6) _p	4.5 (1.7)	4.7 (1.7) _l	5.0 (1.5)	5.0 (1.6) _j
27. Felt angry	4.3 (1.7)	4.3 (1.7) _i	4.4 (1.8)	4.4 (1.7) _g	4.2 (1.6)	4.3 (1.7) _j
30. Felt irritable	4.1 (1.6)	4.2 (1.5) _f	4.2 (1.7)	4.2 (1.5) _g	4.0 (1.5)	4.1 (1.5) _h
31. Lack of understanding from others	4.8 (1.7)	4.9 (1.6) _f	4.8 (1.9)	4.8 (1.6) _g	4.8 (1.6)	4.9 (1.6) _h
32. Satisfied with personal life	3.5 (1.3) _n	3.5 (1.3) _f	3.5 (1.3) _q	3.4 (1.3) _g	3.5 (1.4)	3.6 (1.4) _h
Social function						
4. Unable to attend school/work	4.3 (1.9) _r	4.2 (2.0) _p	4.2 (2.0)	4.3 (1.9) _g	4.4 (1.9) _s	4.2 (2.1) _m
8. Delay/cancel social engagements	4.1 (1.8)	4.1 (1.8) _i	4.0 (1.7)	4.1 (1.8) _l	4.1 (1.8)	4.0 (1.8) _h
12. Difficulty doing leisure/sports	3.0 (1.6)	3.1 (1.7) _f	3.1 (1.6)	3.1 (1.7) _g	2.9 (1.6)	3.1 (1.6) _h
16. Avoid attending events	3.9 (2.1)	3.8 (2.1) _i	4.0 (2.0)	3.9 (2.1) _l	3.8 (2.2)	3.7 (2.0) _h
28. Limited sexual activity	3.9 (2.2) _t	3.8 (2.1) _u	4.1 (2.2) _q	3.7 (2.1) _v	3.8 (2.2) _s	3.8 (2.1) _w

^aN = 229; ^bN = 884; ^cN = 99; ^dN = 400; ^eN = 484; ^fN = 902; ^gN = 415; ^hN = 487; ⁱN = 901; ^jN = 486; ^kN = 899; ^lN = 414; ^mN = 485; ⁿN = 233; ^oN = 129; ^pN = 900; ^qN = 103; ^rN = 232; ^sN = 128; ^tN = 231; ^uN = 895; ^vN = 412; ^wN = 483.
Abbreviations: FAS, full analysis set.

Similarly, large effect sizes were observed for “bowel movements been loose” and “problem with rectal bleeding” at weeks 4 and 8 for TNFi-naïve and TNFi-experienced patients. Additionally, large effect sizes were reported for “bowel

movement frequency” at week 4 (bowel symptoms domain) and “difficulty doing leisure/sports” at week 8 (social function domain) in TNFi-experienced patients. In the TNFi subgroups, all other IBDQ items had small or medium effect sizes, with

TABLE 3. Mean Change From Baseline for Each IBDQ Item in the Overall Population (FAS, Observed Case)

	Week 4		Week 8	
	Placebo (N = 234)	Tofacitinib 10 mg BID (N = 905)	Placebo (N = 234)	Tofacitinib 10 mg BID (N = 905)
Bowel symptoms				
1. Bowel movement frequency, LSM (SE)	1.1 (0.1) _a	2.1 (0.1) _b	1.3 (0.1) _c	2.2 (0.1) _d
Difference vs placebo (95% CI); P value	1.0 (0.7, 1.3); P < 0.0001		0.9 (0.6, 1.2); P < 0.0001	
5. Bowel movements been loose, LSM (SE)	0.7 (0.1) _e	1.8 (0.1) _f	1.0 (0.1) _g	2.1 (0.1) _h
Difference vs placebo (95% CI); P value	1.1 (0.8, 1.3); P < 0.0001		1.1 (0.9, 1.4); P < 0.0001	
9. Troubled by cramps, LSM (SE)	0.6 (0.1) _e	1.3 (0.0) _f	0.8 (0.1) _g	1.4 (0.1) _h
Difference vs placebo (95% CI); P value	0.7 (0.5, 0.9); P < 0.0001		0.6 (0.4, 0.8); P < 0.0001	
13. Troubled by pain, LSM (SE)	0.6 (0.1) _e	1.3 (0.0) _f	0.7 (0.1) _g	1.4 (0.0) _h
Difference vs placebo (95% CI); P value	0.6 (0.4, 0.8); P < 0.0001		0.7 (0.5, 0.9); P < 0.0001	
17. Problems with passing gas, LSM (SE)	0.5 (0.1) _e	0.9 (0.1) _f	0.7 (0.1) _g	1.1 (0.1) _h
Difference vs placebo (95% CI); P value	0.3 (0.1, 0.5); P = 0.0014		0.4 (0.2, 0.6); P = 0.0001	
20. Troubled by bloating, LSM (SE)	0.6 (0.1) _e	0.9 (0.0) _f	0.6 (0.1) _g	1.0 (0.0) _h
Difference vs placebo (95% CI); P value	0.3 (0.1, 0.4); P = 0.0095		0.4 (0.2, 0.6); P < 0.0001	
22. Problem with rectal bleeding, LSM (SE)	1.3 (0.1) _e	2.3 (0.1) _i	1.6 (0.1) _g	2.7 (0.1) _j
Difference vs placebo (95% CI); P value	1.0 (0.7, 1.3); P < 0.0001		1.1 (0.9, 1.4); P < 0.0001	
24. Feeling of having to go, LSM (SE)	0.9 (0.1) _e	1.5 (0.1) _i	1.1 (0.1) _g	1.7 (0.1) _j
Difference vs placebo (95% CI); P value	0.5 (0.3, 0.7); P < 0.0001		0.7 (0.5, 0.9); P < 0.0001	
26. Accidental soiling underpants, LSM (SE)	0.6 (0.1) _e	1.1 (0.0) _k	0.6 (0.1) _g	1.1 (0.0) _i
Difference vs placebo (95% CI); P value	0.4 (0.2, 0.6); P < 0.0001		0.5 (0.4, 0.7); P < 0.0001	
29. Troubled by nausea, LSM (SE)	0.4 (0.1) _e	0.7 (0.0) _f	0.5 (0.1) _g	0.7 (0.0) _h
Difference vs placebo (95% CI); P value	0.3 (0.1, 0.5); P = 0.0004		0.3 (0.1, 0.4); P = 0.0012	
Systemic symptoms				
2. Feeling fatigued or tired, LSM (SE)	0.7 (0.1) _e	1.1 (0.1) _f	0.8 (0.1) _g	1.4 (0.1) _h
Difference vs placebo (95% CI); P value	0.5 (0.3, 0.7); P < 0.0001		0.6 (0.4, 0.8); P < 0.0001	
6. How much energy have you had, LSM (SE)	0.4 (0.1) _e	0.9 (0.0) _f	0.5 (0.1) _m	1.0 (0.0) _h
Difference vs placebo (95% CI); P value	0.4 (0.3, 0.6); P < 0.0001		0.5 (0.4, 0.7); P < 0.0001	
10. Felt generally unwell, LSM (SE)	0.9 (0.1) _e	1.4 (0.1) _n	1.0 (0.1) _g	1.6 (0.1) _j
Difference vs placebo (95% CI); P value	0.5 (0.3, 0.7); P < 0.0001		0.6 (0.4, 0.8); P < 0.0001	
14. Getting good night's sleep, LSM (SE)	0.7 (0.1) _e	1.5 (0.1) _f	0.8 (0.1) _g	1.7 (0.1) _h
Difference vs placebo (95% CI); P value	0.8 (0.6, 1.0); P < 0.0001		0.9 (0.7, 1.1); P < 0.0001	
18. Problem maintaining weight, LSM (SE)	0.3 (0.1) _o	0.6 (0.1) _n	0.4 (0.1) _m	0.7 (0.1) _j
Difference vs placebo (95% CI); P value	0.3 (0.1, 0.5); P = 0.0071		0.3 (0.0, 0.5); P = 0.0215	
Emotional function				
3. Felt frustrated/impatient/restless, LSM (SE)	0.5 (0.1) _e	0.9 (0.0) _f	0.5 (0.1) _g	1.0 (0.0) _h
Difference vs placebo (95% CI); P value	0.4 (0.2, 0.6); P = 0.0002		0.4 (0.2, 0.6); P < 0.0001	
7. Worry about needing surgery, LSM (SE)	0.6 (0.1) _e	1.0 (0.0) _f	0.5 (0.1) _g	1.0 (0.0) _h
Difference vs placebo (95% CI); P value	0.4 (0.2, 0.6); P < 0.0001		0.5 (0.3, 0.7); P < 0.0001	
11. Fear of not finding a washroom, LSM (SE)	0.9 (0.1) _e	1.4 (0.1) _f	0.9 (0.1) _g	1.7 (0.1) _h
Difference vs placebo (95% CI); P value	0.6 (0.3, 0.8); P < 0.0001		0.8 (0.6, 1.0); P < 0.0001	
15. Felt depressed/discouraged, LSM (SE)	0.6 (0.1) _e	1.0 (0.0) _f	0.6 (0.1) _g	1.1 (0.0) _h
Difference vs placebo (95% CI); P value	0.5 (0.3, 0.7); P < 0.0001		0.5 (0.3, 0.7); P < 0.0001	
19. Felt worried or anxious, LSM (SE)	0.8 (0.1) _e	1.2 (0.1) _f	0.9 (0.1) _g	1.4 (0.1) _h
Difference vs placebo (95% CI); P value	0.3 (0.1, 0.5); P = 0.0009		0.5 (0.2, 0.7); P < 0.0001	
21. Felt relaxed/free of tension, LSM (SE)	0.6 (0.1) _e	1.0 (0.1) _i	0.7 (0.1) _g	1.2 (0.1) _j
Difference vs placebo (95% CI); P value	0.3 (0.1, 0.5); P = 0.0009		0.5 (0.3, 0.7); P < 0.0001	
23. Felt embarrassed, LSM (SE)	0.7 (0.1) _e	1.4 (0.1) _i	0.9 (0.1) _g	1.6 (0.1) _j
Difference vs placebo (95% CI); P value	0.6 (0.4, 0.9); P < 0.0001		0.7 (0.5, 0.9); P < 0.0001	

TABLE 3. Continued

	Week 4		Week 8	
	Placebo (N = 234)	Tofacitinib 10 mg BID (N = 905)	Placebo (N = 234)	Tofacitinib 10 mg BID (N = 905)
25. Felt tearful or upset, LSM (SE)	0.5 (0.1) _e	0.8 (0.0) _p	0.5 (0.1) _g	0.8 (0.0) _q
Difference vs placebo (95% CI); P value	0.3 (0.1, 0.5); P = 0.0004		0.3 (0.1, 0.5); P = 0.0008	
27. Felt angry, LSM (SE)	0.4 (0.1) _e	1.1 (0.0) _i	0.5 (0.1) _g	1.1 (0.1) _j
Difference vs placebo (95% CI); P value	0.6 (0.4, 0.8); P < 0.0001		0.6 (0.4, 0.8); P < 0.0001	
30. Felt irritable, LSM (SE)	0.4 (0.1) _e	0.8 (0.0) _f	0.6 (0.1) _g	1.0 (0.0) _h
Difference vs placebo (95% CI); P value	0.4 (0.2, 0.6); P < 0.0001		0.4 (0.2, 0.6); P < 0.0001	
31. Lack of understanding from others, LSM (SE)	0.4 (0.1) _e	0.6 (0.0) _f	0.4 (0.1) _g	0.6 (0.0) _h
Difference vs placebo (95% CI); P value	0.2 (0.1, 0.4); P = 0.0098		0.2 (0.1, 0.4); P = 0.0099	
32. Satisfied with personal life, LSM (SE)	0.4 (0.1) _r	0.7 (0.0) _t	0.6 (0.1) _m	0.9 (0.0) _h
Difference vs placebo (95% CI); P value	0.4 (0.2, 0.5); P < 0.0001		0.3 (0.2, 0.5); P = 0.0001	
Social function				
4. Unable to attend school/work, LSM (SE)	0.7 (0.1) _o	1.1 (0.1) _i	0.7 (0.1) _s	1.4 (0.1) _q
Difference vs placebo (95% CI); P value	0.4 (0.2, 0.6); P = 0.0007		0.7 (0.5, 0.9); P < 0.0001	
8. Delay/cancel social engagements, LSM (SE)	0.8 (0.1) _e	1.4 (0.1) _n	0.8 (0.1) _g	1.5 (0.1) _j
Difference vs placebo (95% CI); P value	0.6 (0.4, 0.8); P < 0.0001		0.8 (0.5, 1.0); P < 0.0001	
12. Difficulty doing leisure/sports, LSM (SE)	0.9 (0.1) _e	1.6 (0.1) _n	1.0 (0.1) _g	2.0 (0.1) _h
Difference vs placebo (95% CI); P value	0.7 (0.5, 0.9); P < 0.0001		1.0 (0.8, 1.2); P < 0.0001	
16. Avoid attending events, LSM (SE)	0.5 (0.1) _e	1.3 (0.1) _n	0.5 (0.1) _g	1.5 (0.1) _j
Difference vs placebo (95% CI); P value	0.8 (0.5, 1.0); P < 0.0001		1.0 (0.7, 1.2); P < 0.0001	
28. Limited sexual activity, LSM (SE)	0.5 (0.1) _t	1.1 (0.1) _u	0.7 (0.1) _v	1.4 (0.1) _w
Difference vs placebo (95% CI); P value	0.7 (0.4, 0.9); P < 0.0001		0.7 (0.4, 0.9); P < 0.0001	

^aN = 227; ^bN = 862; ^cN = 213; ^dN = 832; ^eN = 231; ^fN = 881; ^gN = 218; ^hN = 849; ⁱN = 879; ^jN = 848; ^kN = 877; ^lN = 846; ^mN = 217; ⁿN = 880; ^oN = 229; ^pN = 878; ^qN = 847; ^rN = 230; ^sN = 216; ^tN = 228; ^uN = 872; ^vN = 215; ^wN = 839. Abbreviations: FAS, full analysis set.

the exception of “unable to attend school/work” (social function domain), “lack of understanding from others,” and “felt tearful/upset” (emotional function domain) at week 4 in TNFi-naïve patients and “trouble with bloating” (bowel symptom domain) at week 4 and “problem maintaining weight” and “lack of understanding from others” at weeks 4 and 8 in TNFi-experienced patients, which all had trivial effect sizes (Fig. 3A–D and Supplementary Fig. 1A–D).

DISCUSSION

This pooled post hoc analysis assessed the effect of 10 mg of tofacitinib BID compared with placebo on individual items of the IBDQ. Because the IBDQ has a strong correlation with disease severity, baseline IBDQ scores are valuable in capturing the burden of disease.²¹ In addition, the IBDQ has shown validity and reliability in clinical trials, highlighting that improvements in IBDQ scores reflect improved HRQoL.²¹ Furthermore, IBDQ total scores could potentially be used as a predictor of remission and response in patients with UC, independent of Mayo score–based assessments.²² Our findings may assist with understanding the effects of UC treatment on IBD-specific HRQoL by highlighting which aspects are most likely

to be improved. Furthermore, investigating treatment effects on individual items of the IBDQ in clinical trials may allow study findings to be more relatable to both community physicians and patients. Having a comprehensive understanding of the effect of different UC therapies on IBD-specific aspects of patients’ lives, as determined by analysis of individual IBDQ items, may enable physicians to better tailor treatment to the needs of individual patients in clinical practice.

In the overall population from the pooled OCTAVE Induction studies, significant improvements were observed in each individual IBDQ item with 10 mg of tofacitinib BID vs placebo at week 4 and week 8, which has not been analyzed previously in tofacitinib clinical trials. Significant improvements have previously been reported with 10 mg of tofacitinib BID vs placebo in all 4 IBDQ domains at week 4 and week 8 in the OCTAVE Induction 1 and 2 studies.¹⁶ Furthermore, significant improvements were reported with 5 mg and 10 mg of tofacitinib BID vs placebo in all 4 IBDQ domains at week 8, week 24, and week 52 in the OCTAVE Sustain maintenance study,¹⁶ indicating that the benefit afforded by tofacitinib therapy is durable over this time period. In addition, the results are consistent with the OCTAVE Induction 1 and 2 efficacy analyses,

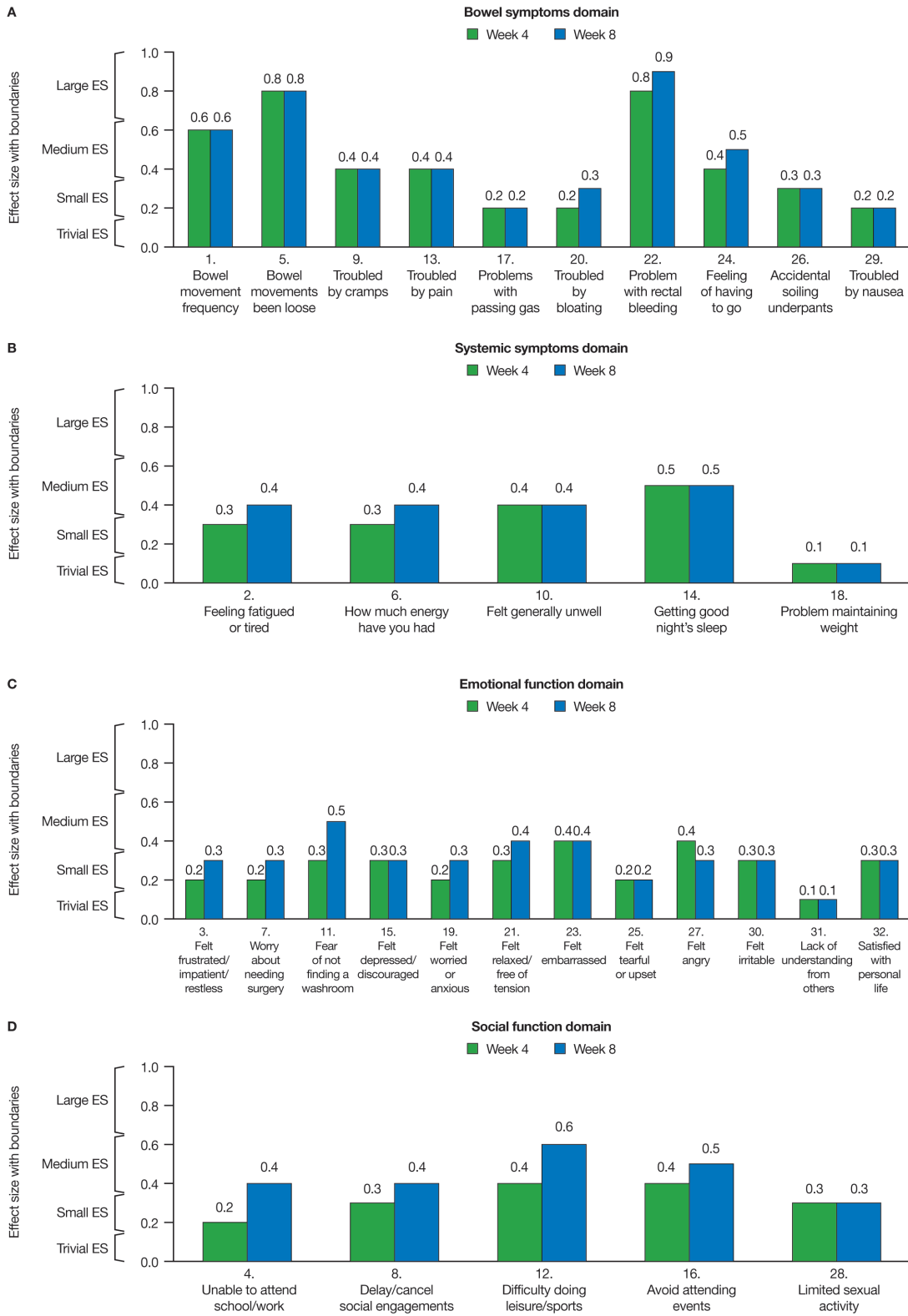


FIGURE 2. Effect sizes of 10 mg of tofacitinib BID vs placebo for the change from baseline for each IBDQ item in the overall population (FAS, observed case). Effect sizes are the difference in least squares means for 10 mg of tofacitinib BID vs placebo, divided by the standard deviation (SD) of baseline scores (where the SD was calculated using data from both treatment groups in both studies); 0.1 = trivial, 0.2 = small, 0.5 = medium, and 0.8 = large. Effect size categorization intervals: 0–0.15, trivial; >0.15–0.35, small; >0.35–0.65, medium; and >0.65, large. Abbreviations: ES effect sizes.

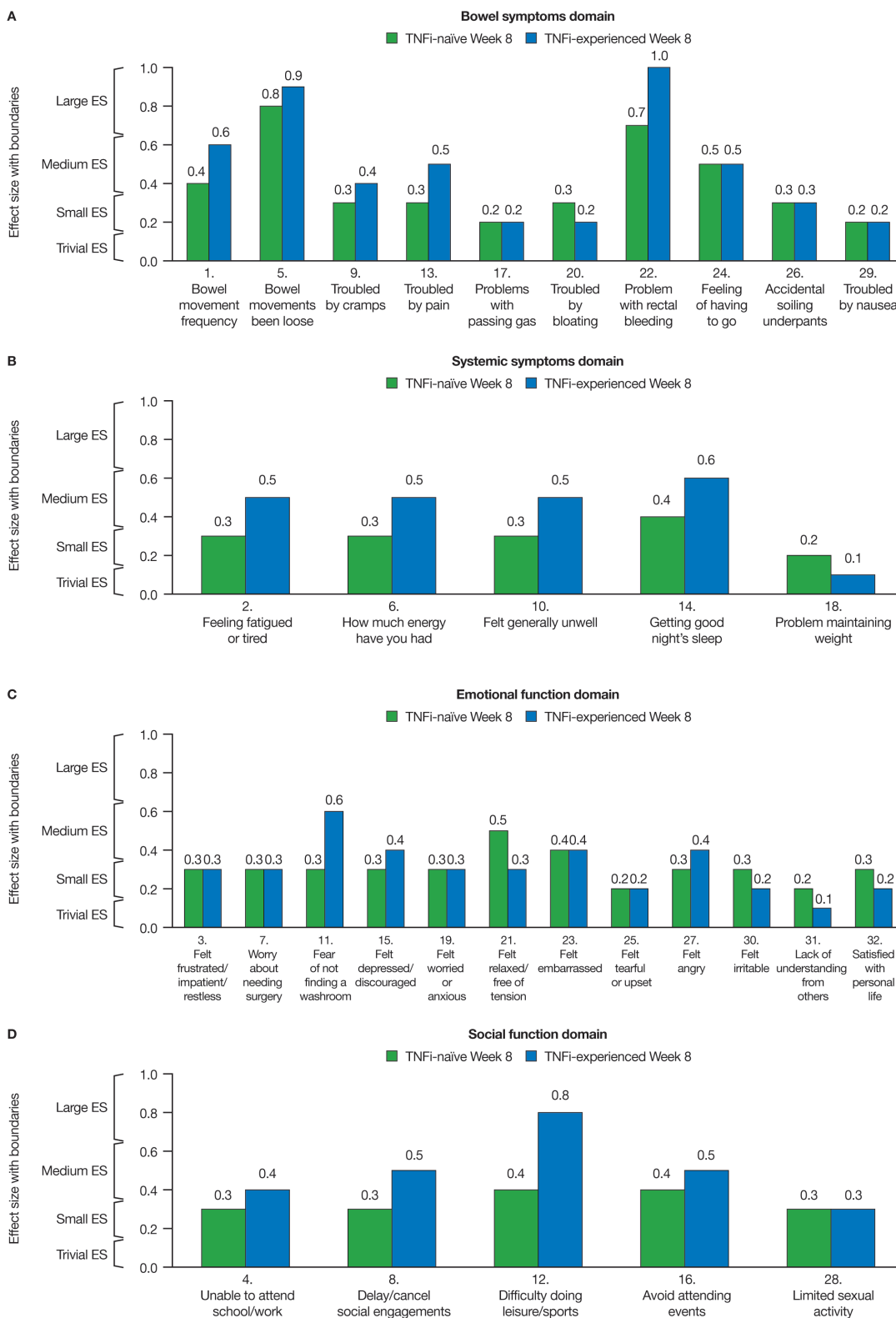


FIGURE 3. Effect sizes of 10 mg of tofacitinib BID vs placebo for the change from baseline for each IBDQ item in TNFi-naïve and TNFi-experienced patients at week 8 (FAS, observed case). Effect sizes are the difference in least squares means for 10 mg of tofacitinib BID vs placebo, divided by the standard deviation (SD) of baseline scores (where the SD was calculated using data from both treatment groups in both studies); 0.1, trivial; 0.2, small; 0.5, medium; and 0.8, large. Effect size categorization intervals: 0–0.15, trivial; >0.15–0.35, small; >0.35–0.65, medium; and >0.65, large. Abbreviations: ES, effect sizes; FAS, full analysis set.

in which the proportion of patients achieving clinical and endoscopic outcomes were significantly improved with induction therapy of 10 mg of tofacitinib BID vs placebo.¹⁴ Effect sizes were generally unchanged between week 4 and week 8 for many of the IBDQ items, indicating that most of the treatment effects with tofacitinib were observed early as patients' inflammatory burden and symptoms improved, with effects then plateauing.

The finding that treatment benefits with 10 mg of tofacitinib BID vs placebo were slightly numerically higher in TNFi-experienced vs TNFi-naïve patients for many IBDQ items is of clinical relevance because TNFi-experienced patients are commonly considered to be more difficult to treat in clinical practice.²³ Previously reported differences in the LSM change from baseline in IBDQ total scores for 10 mg of tofacitinib BID vs placebo at week 8 in OCTAVE Induction 1 and 2 were 15.8 for TNFi-experienced patients and 11.3 for TNFi-naïve patients.¹⁶ Baseline IBDQ item level scores were similar between both TNFi subgroups, and therefore, the numerically higher, placebo-adjusted treatment benefits reported in TNFi-experienced patients for some IBDQ items were not due to these patients having worse HRQoL at baseline but were instead due to the lower placebo response rates that were observed in the TNFi-experienced subpopulation compared with the TNFi-naïve subpopulation.

A limitation of this analysis was that the IBDQ was performed in randomized controlled trials, and therefore, future studies should focus on how these findings extrapolate to the general UC patient population. Although moderate correlations have been reported between IBDQ total scores and Mayo scores from OCTAVE Induction week 8 to OCTAVE Sustain week 52,²² it is unclear how the improvements in individual IBDQ items relate to changes in Mayo scores and with the inflammatory burden of disease. In addition, it needs to be determined how these IBDQ item findings can be applied within clinical practice. Furthermore, this was an ad hoc analysis with no multiplicity adjustment, as the OCTAVE Induction studies were not originally designed to test the individual IBDQ items within each domain. In the subgroup analysis, the high placebo response rate observed in the TNFi-naïve patient population limited the interpretation of these data. Analyses of IBDQ item scores by clinical and endoscopic outcomes would provide a worthwhile extension of the current research.

CONCLUSIONS

In conclusion, significant improvements (nominal P value < 0.05 without multiplicity adjustment) were observed in all bowel-related symptoms, systemic symptoms, emotional functioning, and social functioning IBDQ items with 10 mg of tofacitinib BID vs placebo at both week 4 and week 8, highlighting the broad impact of tofacitinib on all aspects of HRQoL. In the overall population, the greatest numerical

improvements and largest effect sizes across all items were reported for “bowel movements been loose” and “problem with rectal bleeding,” which are both components of the bowel symptom domain and were the most affected at baseline.

Treatment benefits were slightly numerically higher for many IBDQ items in TNFi-experienced patients compared with TNFi-naïve patients. Because this analysis focused on individual IBDQ items, the magnitude of the improvements of individual symptoms and functioning has now been defined, providing an informative and useful perspective on which components of the IBDQ domains are the most improved after tofacitinib induction therapy, which may help to facilitate patient-physician dialogue. This allows the findings from the OCTAVE Induction studies to be more accessible to those who are not overly familiar with the IBDQ, such as community physicians and patients, and may assist with the development of treatment paradigms.

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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DATA SHARING STATEMENT

Upon request and subject to certain criteria, conditions, and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (i) for indications that have been approved in the US and/or EU or (ii) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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