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Health-Related Quality of Life Outcomes With Etrasimod Treatment in Patients With Ulcerative Colitis: A Post Hoc Analysis of Data From ELEVATE UC 52 and ELEVATE UC 12

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Background: Etrasimod is an oral, once-daily (QD), selective sphingosine 1-phosphate$_{1,4,5}$ receptor modulator for the treatment of moderately to severely active ulcerative colitis (UC). Here, we evaluate the impact of etrasimod 2 mg QD on health-related quality of life (HRQoL) in patients with UC.

Methods: This post hoc analysis used data from the Phase 3 randomized controlled trials, ELEVATE UC 52 and ELEVATE UC 12. HRQoL measures included: Inflammatory Bowel Disease Questionnaire (IBDQ), 36-Item Short Form Survey (SF-36), and Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis (WPAI:UC) completed at baseline, Week 12 (both trials), and Week 52 (ELEVATE UC 52 only). For IBDQ analyses, patients were stratified by prior exposure to biologics/Janus kinase inhibitors (JAKi) and baseline modified Mayo score (MMS; 4-6 or 7-9).

Results: Generally, significantly greater proportions of patients receiving etrasimod ($N = 527$) vs placebo ($N = 260$) achieved IBDQ remission (IBDQ total score ≥170) and IBDQ response (IBDQ total score increase from baseline ≥16), with significant improvement in all IBDQ domain scores at Week 12 and maintained through Week 52. Significant differences in IBDQ remission and IBDQ response rates between etrasimod and placebo were more consistent among biologic/JAKi-naive patients vs those who were biologic/JAKi-experienced and in those with baseline MMS 7-9 vs 4-6. Significant improvements were observed in several SF-36 domain and summary scores and WPAI:UC domain scores at Week 12 and Week 52.

Conclusions: Etrasimod 2 mg QD demonstrated significant and clinically meaningful improvements across multiple HRQoL measures, including WPAI, vs placebo.

Clinical Trial Registration: ClinicalTrials.gov: NCT03945188; NCT03996369

Lay Summary

In this analysis of ELEVATE UC 52 and ELEVATE UC 12, we show that etrasimod 2 mg once daily vs placebo demonstrated significant and clinically meaningful improvements in patients' health-related quality of life measured by various instruments.

Key Words: ulcerative colitis, sphingosine 1-phosphate receptor modulator, etrasimod, health-related quality of life

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Key Messages

What is already known?

In addition to conventional targets of ulcerative colitis (UC) treatment, health-related quality of life (HRQoL) and its improvement and normalization are considered important long-term treatment goals.

What is new here?

Using various instruments, we show significant and clinically meaningful improvements in HRQoL in patients receiving etrasimod 2 mg once daily vs placebo at Week 12, which were generally maintained to Week 52.

How can this study help patient care?

We believe this evaluation of a novel, advanced therapy will assist in informing healthcare professionals on available treatment options for patients with UC.

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by mucosal inflammation with continuous distribution and a range of symptoms, including bloody stools, bowel urgency, frequent bowel movements, bowel incontinence, mucus discharge, and fatigue.[1-3] These physical symptoms of UC impact patients' health-related quality of life (HRQoL), affecting their ability to perform everyday tasks, fulfill job functions, and enjoy leisure activities.[4-6] Additionally, most patients with UC (moderate to severe) find it to be disruptive (≤95% of patients), mentally exhausting (≤84% of patients), and more stressful (≤82% of patients) and feel that it controls their lives (>65% of patients) and leads to work absence (≤74% of patients).[7,8] Unsurprisingly, populations with UC tend to have high incidences of anxiety and depression, with rates up to ~60% for both.[7,9-11] As a result, improvement of HRQoL forms an important attribute of UC treatment among patients.[12]

In addition to conventional targets of UC treatment, such as induction and maintenance of clinical remission, endoscopic mucosal healing, and relief of symptoms, HRQoL and its improvement and normalization are now considered an important long-term treatment goal.[13-15] Current treatments for UC include 5-aminosalicylates, corticosteroids, calcineurin inhibitors, immunomodulators (eg, thiopurines), and targeted therapies such as biologics (eg, tumor necrosis factor inhibitors, anti-interleukins [ILs], and anti-integrins) and small molecules (eg, sphingosine 1-phosphate [S1P] receptor modulators and Janus kinase inhibitors [JAKi]).[3,16] However, despite the available and growing number of treatments for UC, many patients still experience adverse effects and a lack of confidence in medications, contributing to decreased adherence.[17,18] As such, patients may have low expectations of improved HRQoL with existing treatments, adding to the many unmet needs for additional therapies.[4,19]

Etrasimod is an oral, once-daily (QD), selective $S1P_{1,4,5}$ receptor modulator for the treatment of moderately to severely active UC. The Phase 3 ELEVATE UC clinical program (comprising ELEVATE UC 52 and ELEVATE UC 12) evaluated the efficacy and safety of etrasimod in patients with moderately to severely active UC.[20] In this program, a greater percentage of patients receiving etrasimod 2 mg QD vs placebo achieved clinical remission (the primary efficacy endpoint) and all key secondary endpoints at Week 12 (both trials).[20]

In this study, using data from the ELEVATE UC 52 and ELEVATE UC 12 trials, we evaluated the impact of etrasimod 2 mg QD vs placebo treatment on disease-specific HRQoL (measured using the Inflammatory Bowel Disease Questionnaire [IBDQ][21]), generic HRQoL (measured using the 36-Item Short Form Survey [SF-36][22]), and work productivity (measured using the Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis [WPAI:UC][23]).

Methods

Study Design and Patient Enrollment

Study design and patient enrollment details have been described previously.[20] In short, ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) were multicenter, randomized, double-blind placebo-controlled trials. ELEVATE UC 52 was a 52-week trial comprising a 12-week induction and 40-week maintenance period; a treat-through design was employed between periods. ELEVATE UC 12 was a 12-week trial (induction only). Eligible patients were adults (16-80 years of age) who had moderately to severely active UC (defined by a modified Mayo score [MMS] of 4-9, which included an endoscopic score ≥2 and rectal bleeding score ≥1). Patients were randomized to receive either etrasimod 2 mg QD or placebo in a 2:1 fashion.

Both trials were performed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines. The trials were approved by the Institutional Review Boards and/or independent ethics committees at each investigational center. All patients provided written informed consent.

Post Hoc Analysis of HRQoL

In both trials, HRQoL measures were completed by patients at baseline and Week 12, with an additional assessment at Week 52 in ELEVATE UC 52.

Inflammatory Bowel Disease Questionnaire

The IBDQ, a validated instrument, consists of 32 items and 4 domains.[21] Items are rated 1-7 (worst function to best function), providing a total score of 32-224 (very poor to very good HRQoL). The 4 domains comprised items specifically assessing bowel symptoms, systemic symptoms, emotional function, and social function.[21] A score of more or equaling 170 points corresponds to clinical remission and is referred to as IBDQ remission; a more than or equaling 16-point increase in IBDQ is an indication of a clinically meaningful improvement and is referred to as an IBDQ response.[24]

Outcomes assessed were IBDQ remission, IBDQ response, and least squares mean (LSM) changes from baseline in IBDQ domain and total scores. Data are presented for patients in each study overall and categorized according to any prior exposure to biologics/JAKi therapy and baseline disease activity (MMS 4-6 or 7-9). Additionally, the proportion of patients who achieved IBDQ and clinical remission or endoscopic improvement at Weeks 12 and 52 were measured. Clinical remission was defined as a stool frequency subscore of 0 (or 1 with a ≥1 point decrease from baseline),

rectal bleeding subscore of 0, and endoscopic subscore (ES) of ≤1 (excluding friability); endoscopic improvement equated an ES of ≤1.

36-Item Short Form Survey

The SF-36 comprises 36 questions evaluating 8 health domains (physical function, role limitations due to physical problems [role physical], role limitations due to emotional problems [role emotional], vitality, mental health, social function, bodily pain, and general health perceptions) which are scored 0-100 (worst possible to best possible). Using the 8 SF-36 domain scores, 2 summary scores can be generated (ie, the physical component summary [PCS] and mental component summary [MCS]) scores).[22] Additionally, by combining all domain scores excluding general health perception, it allows for the generation of the Short-Form Six-Dimension (SF-6D) health utility index (scored 0.0-1.0 [worst to best measured health state]).[25]

Outcomes assessed were mean SF-36 domain scores and LSM changes from baseline in SF-36 PCS and MCS scores and the SF-6D health utility index. Data are presented for patients in each study overall. Using spydergrams, SF-36 data are presented in a simplified format, allowing for the visualization of complex data that form a pattern across all domains.[26]

Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis

The WPAI:UC comprises 6 questions evaluating the impact of UC on 4 domains: absenteeism (missing work), presenteeism (impaired productivity at work), overall work impairment (combined absenteeism and presenteeism), and activity impairment (nonwork activities). Scores are expressed as 0%-100% impairment (less to more impairment) due to disease-specific health problems.[23,27]

Outcomes assessed were LSM changes from baseline in WPAI:UC domain scores. Data are presented for patients in each study overall.

Statistical Analyses

Data were summarized descriptively. For IBDQ remission and response data in both trials, differences (95% CI) and 2-sided *P*-value were based on the Cochran-Mantel-Haenszel method, adjusted according to stratification by biologic/JAKi use at trial entry, baseline corticosteroid use, and baseline disease activity (MMS 4-6 or 7-9). Additionally, the correlation between endpoints for the etrasimod and placebo groups at Weeks 12 (both trials) and 52 (ELEVATE UC 52) were estimated using Cohen's kappa coefficients between IBDQ remission and clinical remission and endoscopic improvement. Kappa coefficient (κ) level of agreement were defined in ranges of agreement: ≤0 (none), 0.01-0.20 (slight), 0.21-0.40 (fair), 0.41-0.60 (moderate), 0.61-0.80 (substantial), and 0.81-1.00 (near-perfect).

For ELEVATE UC 52, LSM changes from baseline in IBDQ domain and total scores, SF-36 domain, summary and SF-6D health utility index scores, and WPAI:UC domain scores were summarized by study drug from a mixed-effect model with repeated measures (MMRM), with a covariate for baseline score, and factors for biologic/JAKi-naive status at study entry, baseline corticosteroid use, baseline disease activity (MMS 4-6 or 7-9), treatment, visit, and treatment-by-visit interaction. Additionally, LSM difference between treatment, 95% CI, and 2-sided *P*-value were estimated from the MMRM.

In ELEVATE UC 12, LSM changes from baseline in IBDQ domain and total scores, SF-36 domain, summary and SF-6D health utility index scores, and WPAI:UC domain scores were summarized by study drug from analysis of covariance model (ANCOVA), with a covariate for baseline score, and factors for naive-to-biologic/JAKi therapy at study entry, baseline corticosteroid use, baseline disease activity (MMS 4-6 or 7-9), and treatment. LSM difference between treatment, 95% CI, and 2-sided nominal *P*-value were estimated from ANCOVA.

Results

Patients

In total, 433 patients received etrasimod or placebo ($N = 289$ and $N = 144$, respectively) in ELEVATE UC 52, and 354 patients received etrasimod or placebo ($N = 238$ and $N = 116$, respectively) in ELEVATE UC 12. Full demographics and baseline disease characteristics for patients in both trials have been reported previously,[20] with key characteristics summarized below. Most patients in both trials were White (ELEVATE UC 52: *n*/*N* = 385/433 [88.9%]; ELEVATE UC 12: *n*/*N* = 264/354 [74.6%]), male (ELEVATE UC 52: *n*/*N* = 240/433 [55.4%]; ELEVATE UC 12: *n*/*N* = 208/354 [58.8%]), and had a median age of 38.0 years (both trials; ELEVATE UC 52: range 17.0-78.0 years; ELEVATE UC 12: range 16.0-73.0 years); baseline characteristics were generally similar between treatment groups.

In ELEVATE UC 52, most patients were biologic/JAKi-naive (etrasimod: *n*/*N* = 205/289 [70.9%]; placebo: *n*/*N* = 99/144 [68.8%]), and a greater proportion had a baseline MMS of 7-9 (etrasimod: *n*/*N* = 176/289 [60.9%]; placebo: *n*/*N* = 87/144 [60.4%]) vs MMS of 4-6 (etrasimod: *n*/*N* = 113/289 [39.1%]; placebo: *n*/*N* = 57/144 [39.6%]). In ELEVATE UC 12, the majority of patients were biologic/JAKi-naive (etrasimod: *n*/*N* = 159/238 [66.8%]; placebo: *n*/*N* = 77/116 [66.4%]), and similar proportions had baseline MMS scores of 4-6 (etrasimod: *n*/*N* = 109/238 [45.8%]; placebo: *n*/*N* = 53/116 [45.7%]) and 7-9 (etrasimod: *n*/*N* = 129/238 [54.2%]; placebo: *n*/*N* = 63/116 [54.3%]).

Baseline values for the HRQoL outcomes of IBDQ domain and total scores, SF-36 domain, summary scores and SF-6D health utility index score, and WPAI-UC domain scores are presented in Table 1 and were generally similar between patients receiving etrasimod and placebo in both trials.

Inflammatory Bowel Disease Questionnaire

In ELEVATE UC 52, significantly more patients receiving etrasimod vs placebo achieved IBDQ remission at Week 12 (42.9% vs 29.2%, respectively; $P = .004$) and maintained at Week 52 (40.5% vs 18.1%, respectively; $P < .0001$; Figure 1A). In ELEVATE UC 12, significantly more patients receiving etrasimod vs placebo achieved IBDQ remission at Week 12 (50.4% vs 31.9%, respectively; $P = .0004$; Figure 1A).

In ELEVATE UC 52, a significantly greater proportion of patients receiving etrasimod vs placebo achieved an IBDQ response at Week 12 (58.5% vs 45.1%, respectively; $P = .009$) and Week 52 (42.9% vs 22.2%, respectively; $P < .0001$; Figure 1B). IBDQ response rates in ELEVATE UC 12 at

Table 1. Baseline HRQoL measures in patients enrolled in ELEVATE UC 52 and ELEVATE UC 12.

	ELEVATE UC 52		ELEVATE UC 12	
	Placebo QD (*N* = 144)	Etrasimod 2 mg QD (*N* = 289)	Placebo QD (*N* = 116)	Etrasimod 2 mg QD (*N* = 238)
IBDQ				
Total score, mean (SD)	119.2 (34.6)	117.5 (34.6)	121.3 (33.4)	125.0 (35.1)
Domain scores, mean (SD)				
Bowel symptoms	35.9 (10.0)	35.2 (10.3)	36.5 (10.6)	37.2 (10.1)
Systemic symptoms	17.8 (5.9)	17.1 (5.8)	17.6 (5.7)	18.6 (6.0)
Social function	19.0 (7.5)	19.1 (7.7)	19.7 (7.1)	20.5 (8.2)
Emotional health	46.4 (14.7)	46.2 (14.5)	47.4 (14.5)	48.7 (14.4)
SF-36				
Domain scores, mean (SD)				
Physical function	69.2 (25.9)	68.2 (24.2)	72.4 (23.0)	73.9 (22.3)
Role physical	49.5 (26.9)	50.3 (25.5)	50.1 (26.1)	53.5 (27.2)
Role emotional	67.0 (27.2)	65.8 (27.1)	64.8 (26.7)	66.0 (27.5)
Vitality	39.9 (22.9)	38.4 (20.1)	41.0 (20.4)	41.1 (21.6)
Mental health	54.5 (21.2)	54.9 (18.9)	55.2 (19.4)	56.4 (20.4)
Social function	54.9 (26.1)	53.0 (25.9)	54.0 (27.5)	56.7 (29.1)
Bodily pain	53.3 (24.2)	49.1 (21.8)	51.0 (21.8)	53.0 (22.3)
General health	40.8 (19.4)	40.5 (19.1)	41.7 (17.6)	39.6 (17.3)
Summary scores, mean (SD)				
Physical component summary	42.7 (8.3)	42.2 (7.8)	43.3 (7.4)	43.7 (7.4)
Mental component summary	40.3 (10.7)	40.0 (10.2)	39.9 (10.7)	40.3 (11.2)
SF-6D health utility index score, mean (SD)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)
WPAI:UC domain scores, mean (SD)				
Absenteeism	19.7 (31.7)	17.6 (28.1)	19.4 (29.5)	20.2 (30.3)
Presenteeism	44.3 (24.5)	45.0 (25.3)	42.9 (24.0)	46.0 (24.3)
Overall work impairment	54.4 (29.2)	55.3 (30.0)	52.1 (28.1)	55.4 (29.1)
Impairment in nonwork activities	49.0 (25.7)	47.5 (25.2)	48.6 (24.2)	47.9 (25.6)

Abbreviations: HRQoL, health-related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; *N*, number of patients in the full analysis set; QD, once daily; SF-36, 36-Item Short Form Survey; SF-6D, Short-Form Six-Dimension; WPAI:UC, Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis.

Week 12 were not significantly different for patients receiving etrasimod vs placebo (Figure 1B).

In ELEVATE UC 52, a greater percentage of patients receiving etrasimod vs placebo achieved IBDQ remission and clinical remission at Week 12 (21.5% vs 6.3%, respectively) and Week 52 (28.0% vs 6.3%, respectively; Supplementary Figure S1A). A fair (Week 12; $\kappa = 0.402$) and substantial (Week 52; $\kappa = 0.637$) agreement in achieving these endpoints was seen for patients receiving etrasimod, while a fair (Week 12; $\kappa = 0.234$) and moderate (Week 52; $\kappa = 0.425$) agreement was seen for patients receiving placebo (Supplementary Figure S1A). Similarly, in ELEVATE UC 12, a greater proportion of patients receiving etrasimod vs placebo achieved IBDQ and clinical remission at Week 12 (20.2% vs 9.5%, respectively; Supplementary Figure S1A). A fair agreement in achieving these endpoints was seen for patients receiving etrasimod ($\kappa = 0.280$) or placebo ($\kappa = 0.258$) at Week 12 (Supplementary Figure S1A).

Furthermore, in ELEVATE UC 52, a greater percentage of patients receiving etrasimod vs placebo achieved IBDQ remission and endoscopic improvement at Week 12 (26.3% vs 11.8%, respectively) and Week 52 (30.8% vs 8.3%, respectively; Supplementary Figure S1B). A moderate (Week 12; $\kappa = 0.426$) and substantial (Week 52; $\kappa = 0.625$) agreement was seen for patients receiving etrasimod, while a fair (Week 12; $\kappa = 0.385$) and moderate (Week 52; $\kappa = 0.449$) agreement was seen for patients receiving placebo (Supplementary Figure S1B). Similarly, in ELEVATE UC 12, a greater percentage of patients receiving etrasimod vs placebo achieved IBDQ remission and endoscopic improvement at Week 12 (24.4% vs 12.1%, respectively; Supplementary Figure S1B). A fair agreement in achieving these endpoints was seen for patients receiving etrasimod ($\kappa = 0.313$) or placebo ($\kappa = 0.311$) at Week 12 (Supplementary Figure S1B). Across all groups, IBDQ remission correlated with clinical remission and endoscopic improvement ($P \leq .002$).

Among biologic/JAKi-naive patients in ELEVATE UC 52, IBDQ remission rates were significantly greater for those receiving etrasimod vs placebo at Week 12 (46.8% vs 32.3%, respectively; $P = .012$) and Week 52 (46.8% vs 21.2%, respectively; $P < .0001$) and in ELEVATE UC 12 at Week 12 (54.1% vs 31.2%, respectively; $P = .0003$; Supplementary Figure S2A). In patients with prior biologic/JAKi experience in ELEVATE UC 52, significantly greater rates of IBDQ remission were not seen among those receiving etrasimod vs placebo at Week 12 but were seen at Week 52 (25.0%

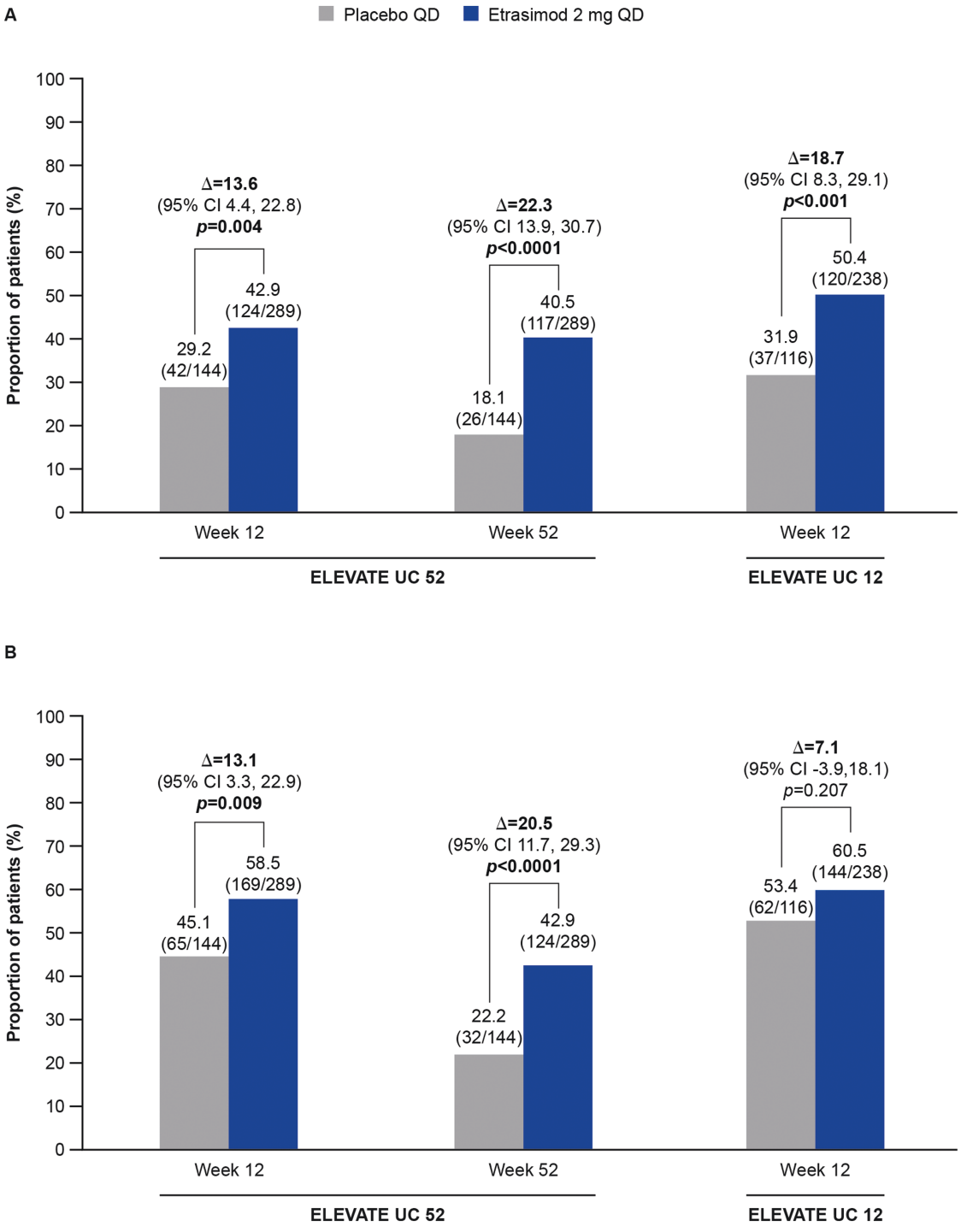


Figure 1. Proportion of patients achieving (A) IBDQ remission (IBDQ ≥ 170) and (B) IBDQ response (IBDQ total score increase from baseline ≥16) at Week 12 and Week 52 in ELEVATE UC 52 and Week 12 in ELEVATE UC 12.Data labels present percentage value with *n*/*N* in brackets underneath. Difference from placebo is adjusted difference. 95% CI and 2-sided *P*-value are based on Cochran-Mantel-Haenszel method adjusting to reported randomization stratification of (1) naive-to-biologic or JAKi therapy at study entry, (2) baseline corticosteroid use, or (3) baseline disease activity (MMS 4-6 or 7-9). Abbreviations: Δ, difference from placebo; IBDQ, Inflammatory Bowel Disease Questionnaire; JAKi, Janus kinase inhibitor; MMS, modified Mayo score; *n*, number of patients; *N*, number of patients in the full analysis set; QD, once daily; UC, ulcerative colitis.

vs 11.1%, respectively; $P = .0425$); remission rates in ELEVATE UC 12 were not significantly different between etrasimod and placebo groups at Week 12 (Supplementary Figure S2A).

Among biologic/JAKi-naive patients in ELEVATE UC 52, IBDQ response rates were significantly greater for the etrasimod vs placebo group at Week 12 (62.4% vs 47.5%, respectively; $P = .012$) and Week 52 (49.8% vs 25.3%, respectively; $P < .0001$); response rates in ELEVATE UC 12 were not significantly different at Week 12 (Supplementary Figure S2B). IBDQ response rates were not significantly different for patients with prior biologic/JAKi experience receiving

etrasimod vs placebo in either trial (Supplementary Figure S2B).

Among patients with baseline MMS 4-6 in ELEVATE UC 52, IBDQ remission rates were not significantly different between etrasimod and placebo groups at Week 12 but were significant at Week 52 (46.0% vs 28.1%, respectively; $P = .018$; Supplementary Figure S3A). IBDQ remission rates among patients with baseline MMS 7-9 in ELEVATE UC 52 were significantly greater in the etrasimod vs placebo group at Week 12 (38.1% vs 19.5%, respectively; $P = .001$) and Week 52 (36.9% vs 11.5%, respectively; $P < .0001$; Supplementary Figure S3A). Among patients with baseline MMS 4-6 in ELEVATE UC 12, IBDQ remission rates were not significantly different between etrasimod and placebo groups at Week 12 but were significant among patients with baseline MMS 7-9 (43.4% vs 19.0%, respectively; $P = .0003$; Supplementary Figure S3A).

Among patients with baseline MMS 4-6 in ELEVATE UC 52, IBDQ response rates were significantly greater for those receiving etrasimod vs placebo at Week 12 (58.4% vs 42.1%, respectively; $P = .039$) and Week 52 (50.4% vs 29.8%, respectively; $P = .0076$). IBDQ response rates among patients with baseline MMS 7-9 in ELEVATE UC 52 were not significantly different between etrasimod vs placebo groups at Week 12 but were significantly different at Week 52 (38.1% vs 17.2%, respectively; $P = .0002$). IBDQ response rates in ELEVATE UC 12 were not significantly different at Week 12 between etrasimod and placebo groups, regardless of baseline MMS (Supplementary Figure S3B).

In ELEVATE UC 52, significantly greater improvements from baseline in LSM IBDQ total scores between etrasimod and placebo groups were seen at Week 12 (42.2 vs 28.1, respectively; $P = .001$) and Week 52 (54.3 vs 36.0, respectively; $P = .002$); LSM change from baseline in IBDQ total score in ELEVATE UC 12 was also significantly greater at Week 12 (46.4 vs 29.0, respectively; $P < .0001$; Supplementary Figure S4). Significantly greater improvements in all LSM IBDQ domain scores from baseline were seen for patients receiving etrasimod vs placebo in ELEVATE UC 52 at Week 12 and Week 52 (Figure 2A) and in ELEVATE UC 12 at Week 12 (Figure 2B).

36-Item Short Form Survey

In ELEVATE UC 52, significantly greater improvements from baseline in LSM PCS scores were observed at Week 12 in the etrasimod vs placebo group (4.83 vs 3.13, respectively; $P = .032$); significantly greater improvements were not continued to Week 52 (Figure 3A). In ELEVATE UC 12, significantly greater improvements from baseline in LSM PCS scores were also observed at Week 12 in the etrasimod vs placebo groups (6.05 vs 3.93, respectively; $P = .006$; Figure 3B). Improvements from baseline in LSM MCS scores in ELEVATE UC 52 were significantly greater for the etrasimod vs placebo groups at Week 12 (6.35 vs 3.62, respectively; $P = .006$) and Week 52 (9.29 vs 6.23, respectively; $P = .028$; Figure 3A); changes in LSM from baseline for MCS scores were also significantly greater in ELEVATE UC 12 at Week 12 (6.52 vs 3.84, respectively; $P = .015$; Figure 3B). In ELEVATE UC 52, significantly greater improvements from baseline in the LSM SF-6D health utility index for patients receiving etrasimod vs placebo were observed at Week 12 (0.08 vs 0.05, respectively; $P = .011$) and Week 52 (0.12 vs 0.07, respectively; $P = .005$; Figure 3A); change in LSM from baseline for SF-6D health utility index was also significantly greater in ELEVATE UC 12 at Week 12 (0.10 vs 0.06, respectively; $P = .002$; Figure 3B).

At Week 12 in ELEVATE UC 52, patients receiving etrasimod vs placebo achieved significantly greater mean SF-36 domain scores ($P < .05$) for role physical, vitality, mental health, bodily pain, and general health (Figure 3A; Supplementary Table S1); at Week 52, mean scores were significantly greater ($P < .05$) for role physical and role emotional (Figure 3A; Supplementary Table S1). At Week 12 in ELEVATE UC 12, patients receiving etrasimod vs placebo achieved significantly greater mean SF-36 domain scores ($P < .05$) for role physical, vitality, mental health, social function, bodily pain, and general health (Figure 3B; Supplementary Table S1).

Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis

In ELEVATE UC 52, significantly greater LSM improvements from baseline were observed for patients receiving etrasimod vs placebo at Week 12 in absenteeism (−13.8 vs −7.0, respectively; $P = .020$), presenteeism (−19.4 vs −11.4, respectively; $P = .043$), and overall work impairment (−25.6 vs −13.3, respectively; $P = .006$). Significantly greater LSM improvements from baseline were only observed at Week 52 for patients receiving etrasimod vs placebo for absenteeism (−16.3 vs −7.0, respectively; $P = .038$; Figure 4A). In ELEVATE UC 12 at Week 12, significantly greater LSM improvements from baseline were observed for patients receiving etrasimod vs placebo in presenteeism (−22.0 vs −12.1, respectively; $P = .016$) and activity impairment (−23.1 vs −11.8, respectively; $P = .002$).

Discussion

This analysis of data from the Phase 3 ELEVATE UC clinical program aimed to evaluate the impact of etrasimod 2 mg QD on patients' HRQoL. Using the IBDQ, SF-36, and WPAI:UC, we showed significant improvements in HRQoL in patients receiving etrasimod vs placebo at Week 12, which were generally maintained to Week 52. The significant improvement in HRQoL outcomes following treatment with etrasimod complements the reported primary and key secondary clinical outcomes of the ELEVATE UC clinical program.[20]

Across trials, a significantly higher percentage of patients achieved IBDQ remission (IBDQ ≥ 170) and IBDQ response (IBDQ total score increase from baseline ≥16) when receiving etrasimod vs placebo; significant improvement was seen in all IBDQ domain scores at Weeks 12 and 52. These significant differences held true for both trials, even with improvements seen in the placebo group. Generally, the percentage of patients achieving IBDQ remission response, as well as improvements in IBDQ domain and total scores, were maintained or improved at Week 52 for patients receiving etrasimod vs placebo in ELEVATE UC 52. The greater improvements observed in IBDQ scores among patients treated with etrasimod vs placebo were consistent with those reported at similar time periods in the OCTAVE (tofacitinib [JAKi]), UNIFI (ustekinumab [IL-12 and IL-23 antibody]), and LUCENT (mirikizumab [IL-23 antibody]) trials.[28-31] However, if using a naive comparison of findings at Week 52, the differences in IBDQ remission and response rates were greater for tofacitinib vs placebo in OCTAVE compared with etrasimod

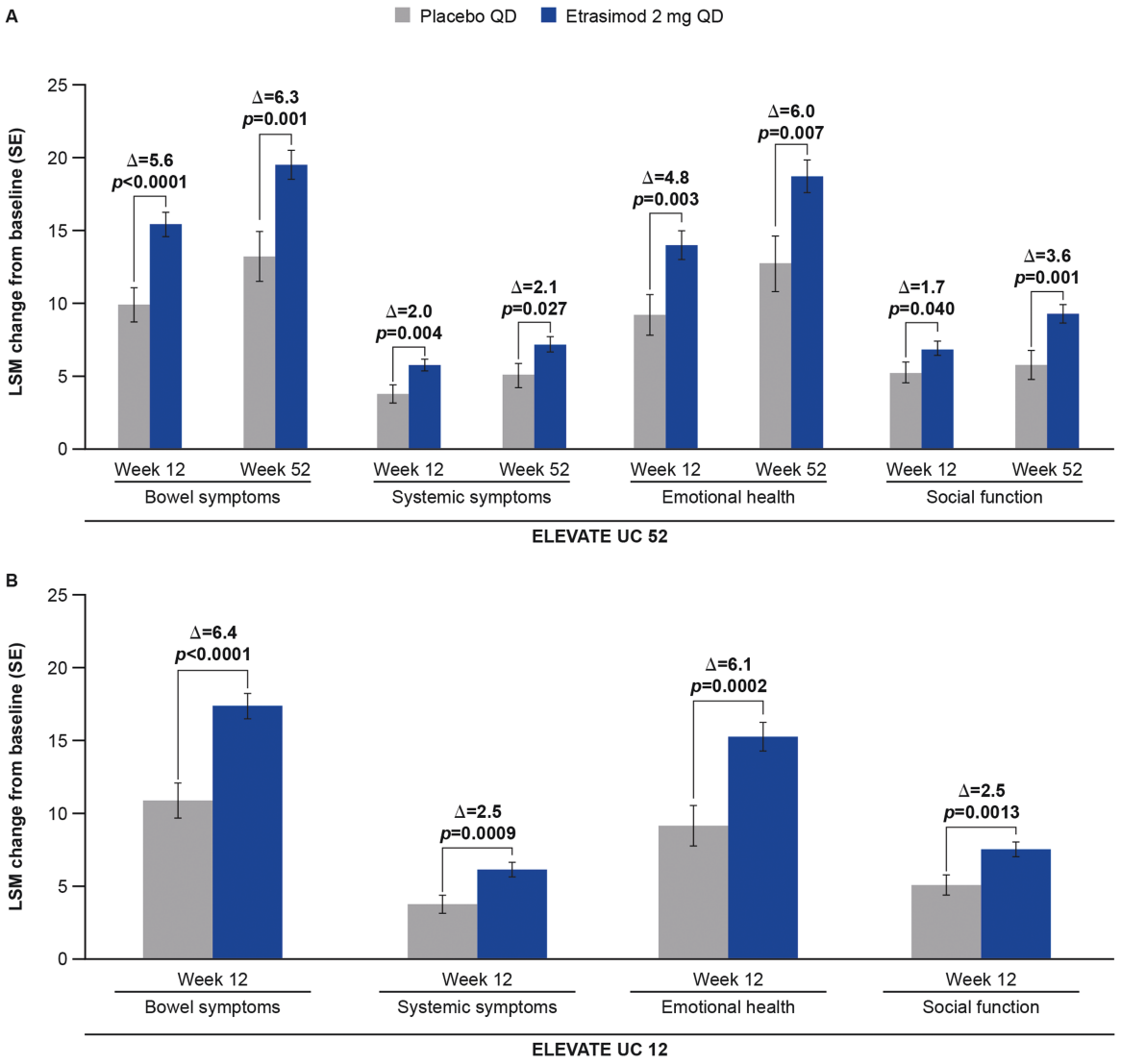
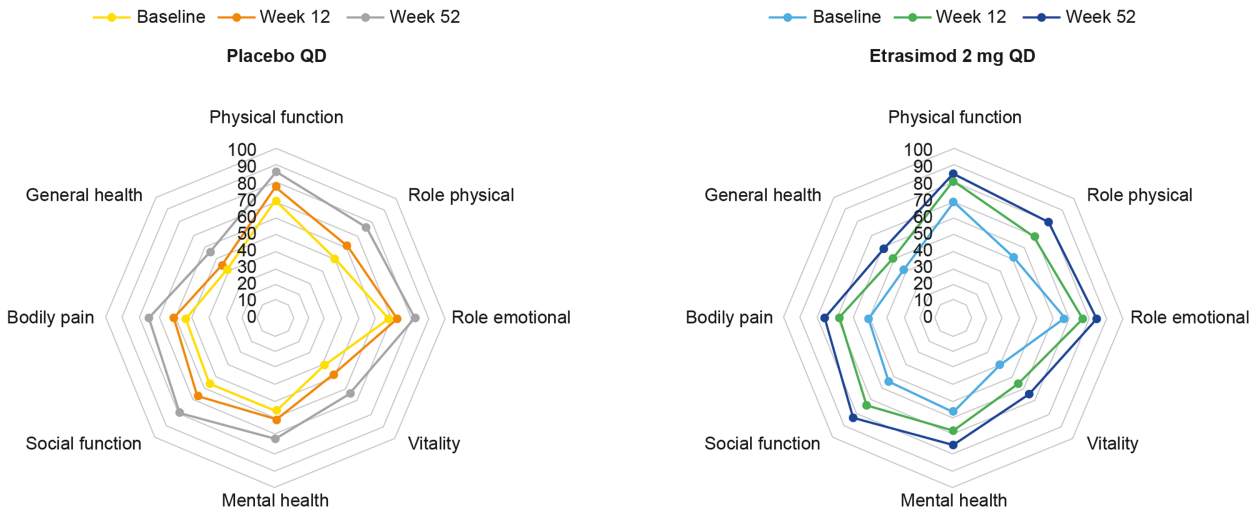


Figure 2. LSM change from baseline and LSM treatment differences in IBDQ domain scores at (A) Week 12 and Week 52 in ELEVATE UC 52 and (B) Week 12 in ELEVATE UC 12.Estimates are from a mixed-effect model with repeated measures (ELEVATE UC 52) and an analysis of covariance model (ELEVATE UC 12) for change from baseline with a covariate for baseline score, and factors for naive-to-biologic/JAKi therapy at study entry (Yes/No), baseline corticosteroid use (Yes/No), baseline disease activity (MMS 4-6 or 7-9), and treatment. Covariates for visit and treatment-by-visit interaction were also included in the mixed-effect model with repeated measures. Abbreviations: Δ, LSM difference between treatments; IBDQ, Inflammatory Bowel Disease Questionnaire; JAKi, Janus kinase inhibitor; LSM, least squares mean; MMS, modified Mayo score; QD, once daily; UC, ulcerative colitis.

vs placebo in ELEVATE UC 52 for this analysis.[28] It should be noted that the design of ELEVATE UC 52, which maintained blinding to Week 52 while allowing responders in the placebo group to remain on treatment, may have contributed to a higher placebo response rate. Additionally, the treat-through design of ELEVATE UC 52 allowed nonresponders, who are less likely to achieve an improvement in HRQoL, to continue etrasimod treatment. Consequently, this design may have diluted the observed percentage difference between placebo and etrasimod groups at Week 52. Therefore, the trial design of ELEVATE UC 52 limits direct comparisons at Week 52 with other trials using a responder rerandomization design. In both trials, more patients achieved IBDQ remission and select efficacy endpoints for etrasimod vs placebo. Additionally, patients receiving etrasimod vs placebo had a greater agreement of achieving these concordant endpoints. These findings support, as shown in other studies,[32] that an improved response to treatment may directly correlate to an increase in HRQoL.

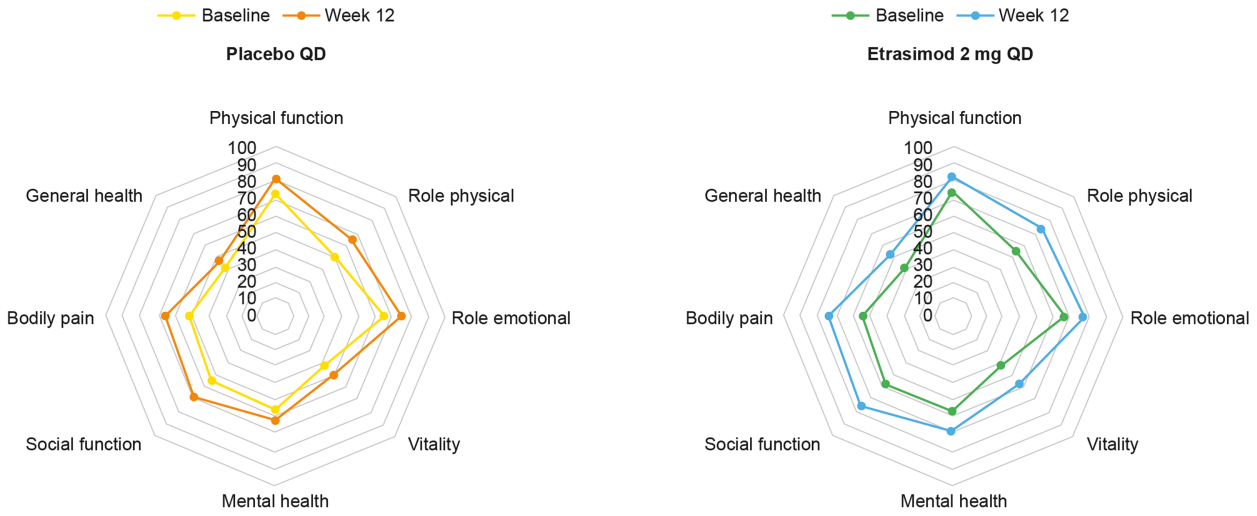
In both trials, differences in IBDQ remission rates between etrasimod and placebo groups were higher for patients with more severe (baseline MMS 7-9) vs moderate (MMS 4-6) disease, which may be attributed to a lower response rate to placebo in patients with more severe disease. Alternatively, the larger difference in IBDQ remission rates between etrasimod and placebo groups may be attributed to patients with more severe disease (baseline MMS 7-9 vs 4-6) generally having lower HRQoL,[33] thus allowing a greater chance for improvement for those treated with etrasimod. IBDQ remission and IBDQ response rates were more consistent between etrasimod and placebo groups and among biologic/JAKi-naive patients vs those with biologic/JAKi experience in both trials. This may be attributed to patients with prior biologic/JAKi experience, representing a more treatment-refractory population;

A



	LSM change at Week 12			LSM change at Week 52		
	Placebo QD	Etrasimod 2 mg QD	*p*-value	Placebo QD	Etrasimod 2 mg QD	*p*-value
PCS score	3.13	4.83	**0.032**	5.24	6.68	0.199
MCS score	3.62	6.35	**0.006**	6.23	9.29	**0.028**
SF-6D health utility index	0.05	0.08	**0.011**	0.07	0.12	**0.005**

B



	LSM change at Week 12		
	Placebo QD	Etrasimod 2 mg QD	*p*-value
PCS score	3.93	6.05	**0.006**
MCS score	3.84	6.52	**0.015**
SF-6D health utility index	0.06	0.10	**0.002**

Figure 3. Actual mean SF-36 domain scores and LSM changes from baseline in PCS and MCS scores and SF-6D health utility index at (A) Week 12 and Week 52 in ELEVATE UC 52 and (B) Week 12 in ELEVATE UC 12.The SF-36 consists of 36 questions measuring 8 health domains which are scored from 0 (worst possible) to 100 (best possible). PCS and MCS measures were calculated using norm-based scoring. The SF-6D health utility index comprises 7 out of the 8 SF-36 domains (scored from 0.0 [worst measured health state] to 1.0 [best measured health state]). Estimates for PCS, MCS, and SF-6D are from mixed-effect model with repeated measures (ELEVATE UC 52) and an analysis of covariance model (ELEVATE UC 12) for change from baseline with a covariate for baseline score, and factors for naive-to-biologic/JAKi therapy at study entry (Yes/No), baseline corticosteroid use (Yes/No), baseline disease activity (MMS 4-6 or 7-9), and treatment. Covariates for visit and treatment-by-visit interaction were also included in the mixed-effect model with repeated measures. Abbreviations: JAKi, Janus kinase inhibitor; QD, once daily; SF-36, 36-Item Short Form Survey; SF-6D, Short-Form Six-Dimension; LSM, least squares mean; MCS, mental component summary; MMS, modified Mayo score; PCS, physical component summary; UC, ulcerative colitis.

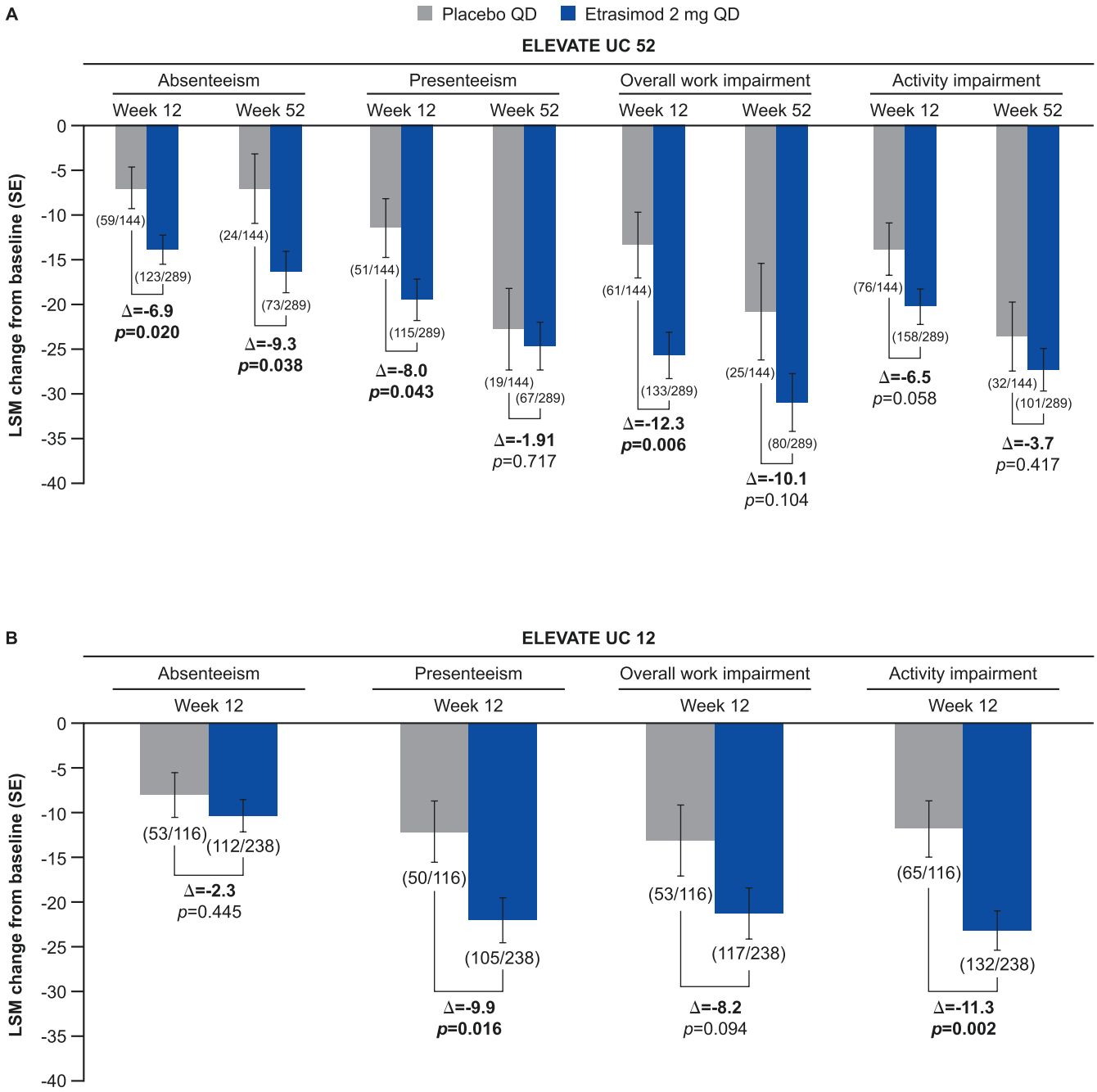


Figure 4. LSM changes from baseline and LSM treatment differences in WPAI:UC domain scores at (A) Week 12 and Week 52 in ELEVATE UC 52 and (B) Week 12 in ELEVATE UC 12. Bracketed data labels are *n*/*N*. The WPAI:UC consists of 6 questions about the effect of UC on 4 domains, each expressed as percentages (0%-100%) of impairment, with lower values indicating less impairment due to disease-specific health problems. Estimates are from a mixed-effect model with repeated measures (ELEVATE UC 52) and an analysis of covariance model (ELEVATE UC 12) with repeated measures model for change from baseline with a covariate for baseline score, and factors for naive-to-biologic/JAKi therapy at study entry (Yes/No), baseline corticosteroid use (Yes/No), baseline disease activity (MMS 4-6 or 7-9), and treatment. Covariates for visit and treatment-by-visit interaction were also included in the mixed-effect model with repeated measures. Abbreviations: Δ, LSM difference between treatments; LSM, least squares mean; *n*, number of patients; *N*, number of patients in the full analysis set; QD, once daily; WPAI:UC, Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis.

however, a significantly higher percentage of patients treated with etrasimod vs placebo achieved IBDQ remission for this subgroup at Week 52 (ELEVATE UC 52). Although this post hoc analysis provides initial insight, additional real-world studies may allow for further subgroup analyses of factors including coexisting mental health conditions, financial status, and occupation. This will aid in predicting which patients may be more likely to achieve improvements in HRQoL.

Patients with active UC have reported deficits in all aspects of functioning and well-being assessed with SF-36, with the largest impact on general health, role physical, and social functioning domains,[34] all of which showed improvements with etrasimod vs placebo in both trials. Improvements in these scores may have substantial impact on HRQoL, as patients with UC often mention decreased work performance, feeling limited in engaging in social activities, and having an

overall feeling that the disease controls their lives.[7,35] Notably, for SF-36 domain scores, improvements with etrasimod vs placebo were generally more pronounced at Week 12 vs Week 52 in ELEVATE UC 52. This may be due to baseline SF-36 domain scores generally being of moderate rating, which, when combined with known ceiling effects of the SF-36 domain scores in patients with UC,[36] may have prevented detecting significant changes at Week 52. Significantly greater improvements in the SF-36 PCS and MCS scores and SF-6D health utility index for etrasimod vs placebo were seen at Week 12, with a more pronounced difference seen in MCS. These findings were complemented by the significantly greater improvements in IBDQ emotional health domain scores with etrasimod vs placebo and are of great importance due to the psychological impact of UC.[9,10]

As both physical and mental health may impact patients' work productivity, findings from SF-36 are supported by results from the WPAI:UC, where etrasimod demonstrated improvements in all domains evaluated at Week 12 in both trials. These findings provide crucial insight into patients' day-to-day living, as work impairment and absenteeism are reported by 40% and 12% of patients with UC, respectively. Additionally, improvements in work impairment may have substantial economic impact, as associated indirect costs are believed to be $24 283 per patient per year in patients with moderately to severely active UC.[27]

This study was limited in that questionnaires were only collected at baseline, Week 12, and Week 52, potentially missing earlier windows and transient changes in HRQoL. Additionally, the small sample size at Week 52 vs Week 12 limited the ability to detect statistically significant differences between treatment groups. Both trials were also active during the COVID-19 pandemic, which has been shown to negatively impact overall HRQoL,[37] potentially impacting HRQoL-related responses in the ELEVATE UC clinical program. Furthermore, the ELEVATE UC trials were not powered to evaluate statistical differences across subgroups of patients. Data were evaluated as part of the statistical analysis plans for ELEVATE UC 52 and ELEVATE UC 12; however, the analyses were not controlled for multiplicity. ELEVATE UC 52 benefited from a treat-through design, allowing insight into patients' HRQoL while receiving uninterrupted etrasimod treatment over a 52-week period. However, the treat-through design limits the comparability with other trial programs due to responders not being rerandomized, potentially increasing the placebo response and decreasing the percentage differences observed between placebo and etrasimod groups towards the end of the maintenance period. The treat-through design also allowed nonresponders to continue, potentially contributing to discontinuations between Week 12 and Week 52, resulting in smaller population sizes for detecting significant differences between treatment groups. Finally, it should be noted that the IBDQ and WPAI:UC questionnaires comprise key disease-specific measures, while SF-36 provides a more generic view of HRQoL. As such, instruments such as the IBDQ provide a more relevant view into patients' treatment experiences.

In conclusion, the efficacy of etrasimod in improving HRQoL among patients with UC in the ELEVATE UC clinical program was shown. Using IBDQ, complemented with WPAI:UC and SF-36, we showed significant, consistent, and clinically meaningful improvements in patients' HRQoL when treated with etrasimod vs placebo. Further instruments that provide UC-specific perspectives of patient experiences to better understand therapies may be an interesting addition to analyses of improvements in HRQoL. Further research should continue to evaluate these findings prospectively in real-world settings following the availability of etrasimod.

Supplementary Data

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

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Author Contributions

A.A., D.T.R., S.S, J.P., and M.C.D.: Investigation. M.F.: Data curation, Methodology, Project administration, Supervision, Visualization, and Writing of the original draft. L.B.: Investigation, Methodology, and Writing of the original draft. D.G.: Investigation and Validation. M.G. and A.B.: Data curation. All authors contributed to the conceptualization and interpretation, and review and editing of the manuscript.

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Conflicts of Interest

A.A. is a consultant/advisor for AbbVie, Allergan, Amgen, Arena, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly, Ferring Pharmaceuticals, Galapagos, Gilead Sciences, Janssen, Lionhealth, MSD, Mylan, Nestlé, Pfizer Inc., Roche, Samsung Bioepis, Sandoz, Takeda, and Tillotts Pharma; was part of the speakers bureau for AbbVie, Amgen, Biogen, Bristol Myers Squibb, Ferring Pharmaceuticals, Eli Lilly, Galapagos, Gilead Sciences, Janssen, Lionhealth, MSD, Novartis, Pfizer Inc., Roche, Samsung Bioepis, Sandoz, Takeda, and TiGenix; and has received grant/research support from Biogen, MSD, Pfizer Inc., and Takeda. D.T.R. is a consultant/advisor for AbbVie, AltruBio, ASLAN Pharmaceuticals, Athos Therapeutics, Bellatrix Pharmaceuticals, Bristol Myers Squibb, Celgene, ClostraBio, Connect BioPharma, Eli Lilly, Iterative Health, Janssen Pharmaceuticals, Pfizer Inc., Prometheus Biosciences, Reistone, Takeda, Target RWE, and Trellus Health; has received grant/research support from GastroIntestinal Research Foundation, Helmsley Charitable Trust, and Takeda; is part of the board of trustees for Cornerstones Health Inc. and Crohn's & Colitis Foundation; and holds stock options for AltruBio, Datos Health, and Iterative Health. S.S. has received consultancy/advisory fees from AbbVie, Arena, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly,

Falk, Fresenius, Gilead Sciences, IMAB, Janssen, MSD, Mylan, Pfizer Inc., Protagonist, Provention Bio, Takeda, Theravance, and Ventyx; and was part of the speakers bureau for AbbVie, Arena, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Falk, Fresenius, Janssen, MSD, Pfizer Inc., and Takeda. J.P. has received grant support/research support from AbbVie and Pfizer Inc.; and has received personal fees from AbbVie, Arena, Athos, Atomwise, Boehringer Ingelheim, Celgene, Celsius, Celltrion, Ferring, Galapagos, Genentech/Roche, GSK, Immunic, Janssen, Mirum, Morphic, Pandion, Pfizer Inc., Progenity, Promethius, Revolo, Sanofi, Takeda, Theravance Biopharma, and Wassermann. M.F. is an employee of Pfizer AG and shareholder of Pfizer Inc. L.B. and D.G. are employees and shareholders of Pfizer Inc. M.G. is an employee and shareholder of Pfizer AG. A.B. is an employee of Pfizer Healthcare India and shareholder of Pfizer Inc. M.C. is a consultant/advisor for Eli Lily, Gilead Sciences, Janssen, Pfizer Inc., Takeda, and Tillotts; has received grant/research support from Galapagos, Janssen, and Pfizer Inc.; is an investigator for AbbVie, Boehringer Ingelheim, Celgene, F Hoffmman La Roche, Genentech, Hospira, Janssen Cilag International LV, Janssen Cilag International NV, Millenium Pharmaceuticals, Shield, Shire, and Takeda; and is the principal investigator for AbbVie, Ferring Pharmaceuticals, Janssen, MSD, and Takeda. M.C.D. has received consultancy/advisory fees from AbbVie, Abivax, Arena Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Genentech, Gilead Sciences, Janssen, Merck Pharmaceuticals, Pfizer Inc., Prometheus Laboratories, Prometheus Biosciences, and Takeda; has received grant/research support from Janssen; is a shareholder/holds royalties for Trellus Health; and holds directorship/ownership interest in Trellus Health.

Data Availability

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

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