Inflammatory Bowel Diseases, 2025, **31**, 2681–2692
https://doi.org/10.1093/ibd/izaf036
Advance access publication 28 February 2025
Original Research Article – Clinical

Efficacy and Safety of Etrasimod in Patients With Moderately to Severely Active Ulcerative Colitis Stratified by Baseline Modified Mayo Score: A Post Hoc Analysis From the Phase 3 ELEVATE UC Clinical Program

Bruce E. Sands, MD,[*] Marla C. Dubinsky, MD,[†] Paulo G. Kotze, MD, MSc, PhD,[‡] Séverine Vermeire, MD, PhD,[§] Remo Panaccione, MD, FRCP,[¶] Millie D. Long, MD, MPH, [ǁ] John C. Woolcott, PhD,[**] Joseph Wu, PhD,[††] Aoibhinn McDonnell, DVM, PhD,[‡‡] Martina Goetsch, MD,[§§] Eustratios Bananis, PhD,[**] and Andres J. Yarur, MD[¶¶]

[*]Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[†]Susan and Leonard Feinstein IBD Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[‡]IBD Outpatient Clinics, Colorectal Surgery Unit, Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, Brazil
[§]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium
[¶]Division of Gastroenterology and Hepatology, Department of Medicine, University of Calgary, Calgary, AB, Canada
[ǁ]Center for Gastrointestinal Biology and Disease, University of North Carolina, Chapel Hill, NC, USA
[**]Pfizer Inc, Collegeville, PA, USA
[††]Pfizer Inc, Cambridge, MA, USA
[‡‡]Pfizer Ltd, Sandwich, UK
[§§]Pfizer AG, Zürich, Switzerland
[¶¶]Inflammatory Bowel Disease Center and Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Address correspondence to: Andres J. Yarur, MD, Inflammatory Bowel Disease Center and Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, USA (Andres.Yarur@cshs.org).

Background: Etrasimod is an oral, once daily, selective sphingosine 1-phosphate $(S1P)_{1,4,5}$ receptor modulator for the treatment of moderately to severely active ulcerative colitis (UC). This post hoc analysis of the ELEVATE UC clinical program describes etrasimod efficacy and safety by patients' baseline disease activity.

Methods: Predefined efficacy endpoints were assessed at week 12 in patients with moderately (modified Mayo score [MMS] 5–7) or severely (MMS 8–9) active UC using pooled data from ELEVATE UC 52 and ELEVATE UC 12. Descriptive statistics with 95% CI were calculated.

Results: Of 743 patients analyzed, 525 (70.7%) had moderately active and 218 (29.3%) had severely active disease at baseline. At week 12, patients treated with etrasimod showed larger mean percentage reductions (95% CI) in MMS vs placebo, regardless of baseline disease activity (−48.4% [−52.3, −44.4] vs −27.0% [−32.2, −21.7] for moderately active disease and −46.4% [−51.2, −41.5] vs −29.8% [−37.2, −22.3] for severely active disease). Similar proportions of patients with moderately or severely active disease treated with etrasimod vs placebo achieved clinical response at week 12 (61.3% vs 39.8% for moderately active disease and 64.5% vs 30.3% for severely active disease). Incidence of treatment-emergent adverse events were similar between disease activity subgroups.

Conclusions: At week 12, etrasimod showed greater reductions in disease activity and higher rates of clinical response vs placebo in patients with either moderately or severely active disease at baseline. The safety profile of etrasimod was consistent with the overall trial population and was unimpacted by baseline disease activity.

ClinicalTrials.gov: NCT03945188; NCT03996369.

Lay Summary

In the ELEVATE UC clinical program, etrasimod treatment of patients with moderately to severely active ulcerative colitis led to greater disease activity reductions and higher clinical response rates vs placebo. The safety profile of etrasimod was unimpacted by baseline disease activity.

Key Words: etrasimod, S1P receptor modulator, ulcerative colitis, disease activity, modified Mayo score

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon and rectum and follows a relapsing and remitting disease course.[1] The goal of treatment is to achieve and maintain long-term clinical, endoscopic, and corticosteroid (CS)-free remission.[2,3] Treatment selection is often guided by the level of disease activity.[2,4,5]

Received for publication: August 19, 2024. Editorial Decision: February 6, 2025

Key Messages

What is already known?

- Etrasimod is efficacious for patients with moderately to severely active ulcerative colitis (UC).

What is new here?

- Patients with either moderately or severely active UC responded equally well to etrasimod. Greater reductions in disease activity and higher clinical response rates vs placebo were observed. The safety profile of etrasimod was unimpacted by baseline disease activity.

How can this study help patient care?

- These findings substantiate the use of etrasimod in patients with UC regardless of disease activity.

The modified Mayo score (MMS) is a composite index of disease activity calculated using the sum of 2 patient-reported outcomes, the rectal bleeding and stool frequency subscores (RBSs; SFSs), and the endoscopic appearance of the mucosa, distinguished using the endoscopic subscore (ES). Each subscore ranges on a scale of 0–3, providing a maximum MMS of 9 with higher scores reflecting severely active disease. The MMS is an evolution of the Mayo score that included the RBS, SFS, ES, and Physician Global Assessment (scored 0–3) with a maximum Mayo score of 12.[6] As part of this evolution, the United States Food and Drug Administration (FDA) has stipulated that an ES of 1 must no longer include mucosal friability.[7] The FDA has provided further classifications on disease activity referring to moderately to severely active UC as an MMS of 5–9, which includes an ES ≥ 2 and mildly to moderately active UC as an MMS of ≤ 4.[8] The European Medicines Agency and FDA both have a recommended definition of clinical remission as an MMS score of 0–2 which includes an SFS of 0–1, an RBS of 0, and a centrally read ES of 0–1.[8,9]

For moderately to severely active UC, approved treatment options include advanced therapies such as biologics (eg, tumor necrosis factor inhibitors and interleukin-23 antagonists[10]) and novel small molecule drugs (eg, Janus kinase inhibitors [JAKi] and sphingosine 1-phosphate [S1P] receptor modulators).[2,4,11–13] The identification of the appropriate treatment course as well as positioning of any novel, advanced therapy in the UC treatment landscape can be assisted by analysis of the therapy's risk-benefit profile, including an understanding of the impact of patients' disease activity on potential treatment response.[2,4]

Etrasimod is an oral, once daily (QD) $S1P_{1,4,5}$ receptor modulator indicated as induction and maintenance therapy for patients with moderately to severely active UC. Efficacy and safety were demonstrated in the global, phase 3 ELEVATE UC 52 and ELEVATE UC 12 clinical trials. During these trials, patients with moderately to severely active UC treated with etrasimod had significant improvements in clinical remission at 12 and 52 weeks.[12]

Previous research has shown that disease activity may impact treatment response to UC therapies.[14] To better understand the impact that disease activity may have on treatment response to etrasimod for patients with UC, this post hoc analysis further explored the efficacy and safety of etrasimod in patients in the ELEVATE UC clinical program. Patients were stratified by baseline disease activity level; disease activity subgroups were further assessed with respect to patients' experience with advanced therapies for UC.

Methods

Patients and Study Design

Both trials were conducted in compliance with the Declaration of Helsinki and were approved by the Institutional Review Boards at each investigational center participating in the studies. All patients provided written informed consent. All authors had access to the study data, and reviewed and approved the final manuscript.

The patient population and study design of the independent ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) trials have been described in detail elsewhere.[12] Briefly, adult patients with moderately to severely active UC (MMS of 4–9 with centrally read ES ≥ 2 and RBS ≥ 1) and a documented history of inadequate response, loss of response, or intolerance of at least one approved UC therapy were eligible to enroll.[12] In both trials, baseline MMS was measured during a 28-day screening period, during which eligibility was determined based on confirmation of an MMS of 4–9. Patients were randomized 2:1 to etrasimod 2 mg QD or placebo QD; randomization was stratified by prior experience with biologic or JAKi therapy (naïve vs experienced), baseline CS use (yes vs no), and baseline disease activity (MMS; 4–6 vs 7–9).

The present post hoc analysis examined the efficacy and safety of etrasimod vs placebo according to patients' disease activity upon entry to the ELEVATE UC clinical program. Patients were stratified into 2 subgroups that reflected moderately active disease, an MMS of 5–7, and severely active disease, an MMS of 8–9. These subgroups were stratified according to patients' prior experience with advanced therapies for UC, namely biologics or JAKi.

Disease Characteristics and Treatment History as Indicators of Treatment Response

To aid in identifying which patients, according to baseline disease activity, are likely to respond when treated with etrasimod, the disease characteristics and treatment history of week 12 clinical responders/nonresponders and remitters/nonremitters were examined.

To assess the potential for inflammatory biomarkers to differentiate between moderately active and severely active disease, concentrations of high-sensitivity C-reactive protein (hsCRP) and fecal calprotectin (FCP) stratified by disease activity subgroup were examined in week 12 clinical responders/nonresponders. Normalization of FCP (100–250 µg/g)[15] was assessed in week 12 responders/nonresponders per disease activity subgroup.

Efficacy Evaluations According to MMS

Details of efficacy evaluations performed in the ELEVATE UC clinical program have been reported previously.[16] For this post hoc analysis, mean continuous percentage change in MMS from baseline to week 12 (data pooled from ELEVATE UC 52 and ELEVATE UC 12) and week 52 (ELEVATE UC 52 only) was assessed. The proportion of patients achieving clinical response, defined as a ≥2-point

and ≥30% decrease in baseline MMS and a ≥1-point decrease from baseline RBS or an RBS ≤ 1, at weeks 12 and 52 according to their baseline MMS was also assessed. Further efficacy endpoints evaluated included clinical remission (defined as an SFS of 0 [or 1 with a ≥1-point decrease from baseline], RBS of 0, and ES of ≤1 [excluding friability]), endoscopic improvement (defined as ES ≤ 1), and endoscopic improvement-histologic remission (EIHR); defined as ES ≤ 1 with histologic remission measured by a Geboes Index score < 2.0, at weeks 12 and 52 according to their baseline MMS.

Additionally, week 12 and week 52 MMS subgroups (MMS 0–2 low; MMS 3–4 mild; MMS 5–7 moderate; MMS 8–9 severe) were examined as multinomial efficacy outcomes, alongside clinical response. Percentage change in MMS from baseline and clinical response according to patients' MMS stratified by prior experience with biologic/JAKi was examined to week 12.

Safety Assessments

Treatment-emergent adverse events (TEAEs) which occurred in >5% of patients in any treatment group, and selected AEs of interest based on Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term (PT) according to patients' baseline disease activity (MMS of 5–7 or MMS of 8–9), were reported. The selected AEs of interest reported are those that have been associated with the treatment of UC by advanced therapies. The ELEVATE UC clinical program further evaluated a number of specific adverse events (AEs) to assess if they met the criteria to be identified as an AE of special interest (AESI). This process of evaluation of potential AESIs involved the review of a subset of reported TEAEs designated Targeted Medical Events and relevant laboratory parameters. This additional medical review determined if an event qualified as an AESI based upon specific AESI criteria.[12]

Statistical Analyses

This post hoc analysis was conducted on the full analysis set (FAS) with baseline MMS 5–9. The FAS includes patients who were randomized and received at least one dose of the study treatment. Analyses were stratified into 2 subgroups reflecting baseline disease activity, either moderately active (MMS of 5–7) or severely active (MMS of 8–9), and further stratified by prior experience with biologic/JAKi (experienced or naïve). Efficacy and safety data to week 12 were pooled from ELEVATE UC 52 and ELEVATE UC 12, and reported to week 52 for ELEVATE UC 52 only. Baseline demographics and clinical characteristics by MMS subgroup were summarized descriptively.

Descriptive statistics were reported by treatment group and baseline disease activity (MMS) subgroup categories. Multinomial efficacy outcomes such as the count of responders and proportions had simultaneous 95% CIs calculated via the Goodman method.[17] Continuous efficacy endpoints such as means and medians and 95% CIs of the means were calculated and descriptively summarized assuming a normal distribution. Any missing response was considered as non-response for all binary endpoints. Missing continuous endpoints were not imputed. Missing demographics, baseline characteristics, and safety endpoints were not imputed. Descriptive statistics were reported for safety endpoints such as incidence rates per 100 patient-years of TEAEs by treatment group.

Results

Patient Demographics and Disease Characteristics

The FAS, comprising patients pooled from ELEVATE UC 52 and ELEVATE UC 12, included a total of 743 patients; 496 and 247 were randomized to receive etrasimod and placebo, respectively. Of these, 525 (70.7%) had moderately active disease (MMS of 5–7) and 218 (29.3%) had severely active disease (MMS of 8–9) at trial baseline. Demographics were generally similar between subgroups (Table 1), although, as expected, higher proportions of patients had an ES of 3, with higher median FCP and hsCRP concentrations at baseline in the severely active disease subgroup vs the moderately active disease subgroup, reflecting disease activity as measured by these objective measures (Table 1). Higher proportions of isolated proctitis (centrally read) were observed in patients with moderately active vs severely active disease (9.3% vs 3.3% and 9.4% vs 3.0% in etrasimod and placebo treatment groups, respectively [Table 1]).

Disease Characteristics and Treatment History According to Disease Severity at Baseline as Indicators of Clinical Response

With respect to the achievement of clinical response at week 12, disease characteristics and treatment history were generally similar between responders and nonresponders. However, a higher proportion of treatment responders vs nonresponders with moderately active disease at baseline had an ES of 2 vs an ES of 3 at baseline (Table 2). Regardless of baseline disease activity (moderately or severely active), a higher proportion of treatment nonresponders had prior experience with >1 biologic/JAKi compared with treatment responders in most treatment subgroups (Table 2). Patient demographics were generally balanced between responder vs nonresponder subgroups (Table S1).

At week 12, median concentrations of FCP were higher in the severely active vs moderately active disease at baseline subgroup for both clinical responders and nonresponders. The greatest median reduction from baseline in FCP concentration (–550.9 µg/g) at week 12 was observed in responders treated with etrasimod who had moderately active disease at baseline (Table S2). In the baseline MMS 5–7 subgroup, 64.6% (n = 122, $N1$ [number of patients with observations at the visit] = 189) of responders and 21.7% (n = 20, $N1$ = 92) of nonresponders treated with etrasimod vs 50.8% (n = 31, $N1$ = 61) of responders and 18.6% (n = 16, $N1$ = 86) of nonresponders treated with placebo reached the threshold of 250 µg/g. This pattern was consistent with the baseline MMS 8–9 subgroup, of which 46.0% (n = 40, $N1$ = 87) of responders and 10.5% (n = 4, $N1$ = 38) of nonresponders treated with etrasimod vs 27.8% (n = 5, $N1$ = 18) of responders and 10.5% (n = 4, $N1$ = 38) of nonresponders treated with placebo reached the threshold by week 12 (Table S2).

Median concentrations of hsCRP were higher in the baseline moderately active disease subgroup vs the baseline severely active disease subgroup. The greatest median reduction from baseline in hsCRP concentrations was observed in responders treated with etrasimod in the severely active disease at baseline subgroup, although this was less pronounced in the moderately active disease at baseline subgroup (Table S2).

Table 1. Demographics and baseline characteristics of patients in the ELEVATE UC clinical program[a] stratified according to baseline disease activity (moderately active: MMS 5–7; severely active: MMS 8–9).

	Baseline MMS 5–7		Baseline MMS 8–9	
	Etrasimod 2 mg QD (*N* = 344)	Placebo QD (*N* = 181)	Etrasimod 2 mg QD (*N* = 152)	Placebo QD (*N* = 66)
Age (years), mean (SD)	40.6 (13.9)	40.3 (13.9)	42.2 (13.8)	37.6 (12.9)
Female, *n* (%)	158 (45.9)	70 (38.7)	69 (45.4)	27 (40.9)
Race, *n* (%)				
White	278 (80.8)	154 (85.1)	132 (86.8)	53 (80.3)
Asian	45 (13.1)	21 (11.6)	16 (10.5)	10 (15.2)
Black or African American	7 (2.0)	2 (1.1)	1 (0.7)	3 (4.5)
Other[b]	14 (4.1)	4 (2.2)	3 (2.0)	0
Duration of UC (years), mean (SD)	7.5 (7.5)	7.0 (6.7)	7.3 (7.1)	6.4 (6.1)
Isolated proctitis,[c] *n* (%)	32 (9.3)	17 (9.4)	5 (3.3)	2 (3.0)
Baseline MMS, mean (SD)	6.3 (0.8)	6.3 (0.7)	8.1 (0.2)	8.1 (0.3)
ES of 3 at baseline, *n* (%)	144 (41.9)	86 (47.5)	145 (95.4)	62 (93.9)
Baseline CS use, *n* (%)	89 (25.9)	53 (29.3)	58 (38.2)	19 (28.8)
Naïve to prior biologic/JAKi, *n* (%)	240 (69.8)	126 (69.6)	102 (67.1)	41 (62.1)
FCP (µg/g)				
*N*1	342	179	151	65
Median (Q1, Q3)	929.2 (304.4, 2218.0)	899.9 (235.0, 2298.1)	1308.3 (458.9, 2789.0)	1281.1 (503.9, 3465.4)
hsCRP (mg/L)				
*N*1	344	181	152	66
Median (Q1, Q3)	3.0 (1.1, 8.5)	2.7 (1.0, 7.3)	5.6 (3.1, 11.0)	5.3 (2.4, 14.3)

[a]Pooled for ELEVATE UC 52 and ELEVATE UC 12.
[b]Other included American Indian or Alaska Native, Multiple, and Not Reported.
[c]Centrally read.
Abbreviations: CS, corticosteroid; ES, endoscopic subscore; FCP, fecal calprotectin; hsCRP, high-sensitivity C-reactive protein; JAKi, Janus kinase inhibitor; MMS, modified Mayo score; *N*, number of patients in the baseline disease activity subgroup by treatment; *N*1, number of patients with evaluable observations at baseline; *n*, number of patients in the specified category; Q1, first quartile; Q3, third quartile; QD, once daily; SD, standard deviation; UC, ulcerative colitis.

Disease Characteristics and Treatment History According to Disease Severity at Baseline as Indicators of Week 12 Clinical Remission

Higher proportions of patients with severely active disease had an RBS of 3, ES of 3, and SFS of 3 at baseline compared to moderately active disease; however, these characteristics were similar between week 12 remitters (patients in clinical remission) and nonremitters (Table 3). Of patients with moderately active disease, higher proportions of remitters vs nonremitters had an ES of 2 vs an ES of 3 at baseline (Table 3).

The proportions of nonremitters with prior experience with >1 biologic/JAKi were higher than the proportions of remitters with prior experience with >1 biologic/JAKi, regardless of baseline disease activity for most subgroups (Table 3). Patient demographics were generally balanced between remitter vs non-remitter subgroups (Table S3).

Efficacy Assessments

At week 12, patients treated with etrasimod demonstrated larger mean percentage reductions in MMS vs placebo, regardless of baseline disease activity (moderately active [MMS 5–7]: –48.4% [95% CI, –52.3 to –44.4] vs –27.0% [95% CI, –32.2 to –21.7]; severely active [MMS 8–9]: –46.4% [95% CI, –51.2 to –41.5] vs –29.8% [95% CI, –37.2 to –22.3]) (Figure 1). These observations were consistent when data were further stratified by prior experience with biologic/JAKi, although the reductions in MMS vs placebo were less pronounced in patients with severely active disease at baseline (MMS 8–9) and prior experience with biologic/JAKi, for whom the percentage change from baseline MMS at week 12 was comparable in those who received etrasimod (–38.5%) or placebo (–33.0%) (Figure 1).

At week 12, more patients treated with etrasimod achieved clinical response vs placebo (Figure 2). Of patients with moderately active disease at baseline, 61.3% (95% CI, 56.2 to 66.5) vs 39.8% (95% CI, 32.6 to 46.9) treated with etrasimod vs placebo achieved clinical response at week 12, respectively. Similarly, for patients with severely active disease at baseline, 64.5% (95% CI, 56.9 to 72.1) vs 30.3% (95% CI, 19.2 to 41.4) treated with etrasimod vs placebo achieved clinical response at week 12 (Figure 2). This trend was observed at week 52, at which point 48.7% (95% CI, 41.6 to 55.8) of patients treated with etrasimod and 26.3% (95% CI, 17.6 to 34.9) of patients treated with placebo achieved clinical response in the moderately active disease at baseline subgroup, and 47.1% (95% CI, 36.4 to 57.7) of patients treated with etrasimod and 13.9% (95% CI, 2.6

Table 2. Disease characteristics and treatment history of responders vs nonresponders in clinical response at week 12 according to disease activity at baseline (moderately active: MMS 5–7; severely active: MMS 8–9) in pooled data from ELEVATE UC 52 and ELEVATE UC 12.

	Baseline MMS 5–7				Baseline MMS 8–9			
	Clinical responders		Clinical nonresponders		Clinical responders		Clinical nonresponders	
	Etrasimod 2 mg QD (*N* = 211)	Placebo QD (*N* = 72)	Etrasimod 2 mg QD (*N* = 133)	Placebo QD (*N* = 109)	Etrasimod 2 mg QD (*N* = 98)	Placebo QD (*N* = 20)	Etrasimod 2 mg QD (*N* = 54)	Placebo QD (*N* = 46)
Extent of UC, *n* (%)								
Left-sided colitis/proctosigmoiditis[a]	131 (62.4)	39 (54.2)	61 (46.2)	60 (55.6)	71 (72.4)	13 (65.0)	33 (61.1)	30 (65.2)
Pancolitis[a]	59 (28.1)	26 (36.1)	63 (47.7)	41 (38.0)	25 (25.5)	7 (35.0)	20 (37.0)	13 (28.3)
Isolated proctitis[b]	25 (11.8)	7 (9.7)	7 (5.3)	10 (9.2)	2 (2.0)	0	3 (5.6)	2 (4.3)
MMS and subscores at baseline								
Baseline MMS, mean (SD)	6.2 (0.7)	6.3 (0.7)	6.4 (0.8)	6.3 (0.7)	8.0 (0.2)	8.2 (0.4)	8.1 (0.3)	8.1 (0.3)
Baseline RBS, *n* (%)								
1	95 (45.0)	30 (41.7)	76 (57.1)	56 (51.4)	0	0	0	0
2	109 (51.7)	42 (58.3)	55 (41.4)	53 (48.6)	86 (87.8)	15 (75.0)	44 (81.5)	40 (87.0)
3	7 (3.3)	0	2 (1.5)	0	12 (12.2)	5 (25.0)	10 (18.5)	6 (13.0)
Baseline SFS, *n* (%)								
0	1 (0.5)	0	1 (0.8)	0	0	0	0	0
1	20 (9.5)	4 (5.6)	14 (10.5)	17 (15.6)	0	0	0	0
2	114 (54.0)	40 (55.6)	49 (36.8)	45 (41.3)	4 (4.1)	0	1 (1.9)	0
3	76 (36.0)	28 (38.9)	69 (51.9)	47 (43.1)	94 (95.9)	20 (100.0)	53 (98.1)	46 (100.0)
Baseline ES, *n* (%)								
2	139 (65.9)	48 (66.7)	61 (45.9)	47 (43.1)	5 (5.1)	2 (10.0)	2 (3.7)	2 (4.3)
3	72 (34.1)	24 (33.3)	72 (54.1)	62 (56.9)	93 (94.9)	18 (90.0)	52 (96.3)	44 (95.7)
Treatment history								
Baseline CS use, *n* (%)	56 (26.5)	27 (37.5)	33 (24.8)	26 (23.9)	35 (35.7)	6 (30.0)	23 (42.6)	13 (28.3)
Naïve to prior biologic/JAKi, *n* (%)	159 (75.4)	54 (75.0)	81 (60.9)	72 (66.1)	70 (71.4)	13 (65.0)	32 (59.3)	28 (60.9)
Number of prior biologic/JAKi								
0	159 (75.4)	54 (75.0)	81 (60.9)	72 (66.1)	70 (71.4)	13 (65.0)	32 (59.3)	28 (60.9)
1	26 (12.3)	10 (13.9)	24 (18.0)	21 (19.3)	14 (14.3)	1 (5.0)	11 (20.4)	12 (26.1)
>1	26 (12.3)	8 (11.1)	28 (21.1)	16 (14.7)	14 (14.3)	6 (30.0)	11 (20.4)	6 (13.0)
Prior oral 5-ASA compound use, *n* (%)	40 (19.0)	12 (16.7)	15 (11.3)	21 (19.3)	8 (8.2)	1 (5.0)	4 (7.4)	4 (8.7)
Prior immunomodulators, *n* (%)	70 (33.2)	22 (30.6)	57 (42.9)	43 (39.4)	34 (34.7)	9 (45.0)	26 (48.1)	17 (37.0)

[a]Left-sided colitis and pancolitis were entered by investigators.
[b]Isolated proctitis was centrally read.
Abbreviations: 5-ASA, 5-aminosalicylates; CS, corticosteroid; ES, endoscopic subscore; JAKi, Janus kinase inhibitor; MMS, modified Mayo score; *N*, number of patients in the baseline disease activity subgroup by treatment; *n*, number of patients in the specified category; QD, once daily; RBS, rectal bleeding subscore; SD, standard deviation; SFS, stool frequency subscore; UC, ulcerative colitis.

to 25.2) of patients treated with placebo achieved clinical response in the severely active disease at baseline subgroup (Table S4).

With respect to clinical remission, patients with moderately active disease at baseline, 29.9% vs 12.2% treated with etrasimod vs placebo achieved clinical remission at week 12; for patients with severely active disease at baseline, 17.1% vs 7.6% achieved clinical remission at week 12. At week 52, 32.3% vs 8.1% of patients with moderately active disease at baseline who received etrasimod vs placebo, respectively, achieved clinical remission; for patients with severely active disease at baseline 31.8% vs 2.8% who received etrasimod vs placebo, respectively, achieved this endpoint (Figure S1).

At week 12, a greater proportion of patients with moderately active than severely active disease at baseline achieved endoscopic improvement (moderately active [MMS: 5–7]: 39.2% vs 17.1%; severely active [MMS: 8–9]: 19.1% vs 13.6% for etrasimod vs placebo, respectively). This trend continued at week 52 (moderately active [MMS: 5–7]: 39.2% vs 12.1%; severely active [MMS: 8–9]: 32.9% vs 5.6% for etrasimod vs placebo, respectively) (Figure S2).

At week 12, a higher proportion of patients with moderately active than severely active disease at baseline achieved EIHR (moderately active [MMS: 5–7]: 22.4% vs 6.6%; severely active [MMS: 8–9]: 11.2% vs 6.1% for etrasimod vs placebo, respectively). Proportions of patients achieving EIHR at week 52 were higher in the moderately active disease at baseline subgroup (moderately active [MMS: 5–7]: 29.1% vs 10.1%, severely active [MMS: 8–9]: 21.2% vs 2.8% for etrasimod vs placebo, respectively) (Figure S3).

With respect to patients with moderately active disease at baseline achieving an MMS of 0–2 at week 12, this was accomplished by 38.4% (95% CI, 31.9 to 45.3) and 17.1% (95% CI, 11.1 to 25.5) of those treated with etrasimod and

Table 3. Disease characteristics and treatment history of remitters vs nonremitters at week 12 according to baseline disease activity (moderately active: MMS 5–7; severely active: MMS 8–9) in pooled data from ELEVATE UC 52 and ELEVATE UC 12.

	Baseline MMS 5–7				Baseline MMS 8–9			
	Clinical remitters		Clinical nonremitters		Clinical remitters		Clinical nonremitters	
	Etrasimod 2 mg QD (*N* = 103)	Placebo QD (*N* = 22)	Etrasimod 2 mg QD (*N* = 241)	Placebo QD (*N* = 159)	Etrasimod 2 mg QD (*N* = 26)	Placebo QD (*N* = 5)	Etrasimod 2 mg QD (*N* = 126)	Placebo QD (*N* = 61)
Extent of UC, *n* (%)								
Left-sided colitis/proctosigmoiditis[a]	62 (60.2)	12 (54.5)	130 (54.4)	87 (55.1)	16 (61.5)	2 (40.0)	88 (69.8)	41 (67.2)
Pancolitis[a]	29 (28.2)	9 (40.9)	93 (38.9)	58 (36.7)	8 (30.8)	3 (60.0)	37 (29.4)	17 (27.9)
Isolated proctitis[b]	16 (15.5)	3 (13.6)	16 (6.6)	14 (8.8)	0	0	5 (4.0)	2 (3.3)
MMS and subscores at baseline								
Baseline MMS, mean (SD)	6.1 (0.8)	6.0 (0.9)	6.3 (0.7)	6.4 (0.7)	8.0 (0.0)	8.0 (0.0)	8.1 (0.3)	8.1 (0.3)
Baseline RBS, *n* (%)								
1	49 (47.6)	12 (54.5)	122 (50.6)	74 (46.5)	0	0	0	0
2	51 (49.5)	10 (45.5)	113 (46.9)	85 (53.5)	20 (76.9)	5 (100.0)	110 (87.3)	50 (82.0)
3	3 (2.9)	0	6 (2.5)	0	6 (23.1)	0	16 (12.7)	11 (18.0)
Baseline SFS, *n* (%)								
0	0	0	2 (0.8)	0	0	0	0	0
1	8 (7.8)	1 (4.5)	26 (10.8)	20 (12.6)	0	0	0	0
2	61 (59.2)	13 (59.1)	102 (42.3)	72 (45.3)	3 (11.5)	0	2 (1.6)	0
3	34 (33.0)	8 (36.4)	111 (46.1)	67 (42.1)	23 (88.5)	5 (100.0)	124 (98.4)	61 (100.0)
Baseline ES, *n* (%)								
2	74 (71.8)	18 (81.8)	126 (52.3)	77 (48.4)	3 (11.5)	0	4 (3.2)	4 (6.6)
3	29 (28.2)	4 (18.2)	115 (47.7)	82 (51.6)	23 (88.5)	5 (100.0)	122 (96.8)	57 (93.4)
Treatment history								
Baseline CS use, *n* (%)	32 (31.1)	12 (54.5)	57 (23.7)	41 (25.8)	12 (46.2)	2 (40.0)	46 (36.5)	17 (27.9)
Naïve to prior biologic/JAKi, *n* (%)	80 (77.7)	18 (81.8)	160 (66.4)	108 (67.9)	21 (80.8)	3 (60.0)	81 (64.3)	38 (62.3)
Number of prior biologic/JAKi use								
0	80 (77.7)	18 (81.8)	160 (66.4)	108 (67.9)	21 (80.8)	3 (60.0)	81 (64.3)	38 (62.3)
1	13 (12.6)	2 (9.1)	37 (15.4)	29 (18.2)	4 (15.4)	0	21 (16.7)	13 (21.3)
>1	10 (9.7)	2 (9.1)	44 (18.3)	22 (13.8)	1 (3.8)	2 (40.0)	24 (19.0)	10 (16.4)
Prior oral 5-ASA compound use, *n* (%)	23 (22.3)	2 (9.1)	32 (13.3)	31 (19.5)	2 (7.7)	0	10 (7.9)	5 (8.2)
Prior immunomodulators use, *n* (%)	32 (31.1)	7 (31.8)	95 (39.4)	58 (36.5)	11 (42.3)	2 (40.0)	49 (38.9)	24 (39.3)

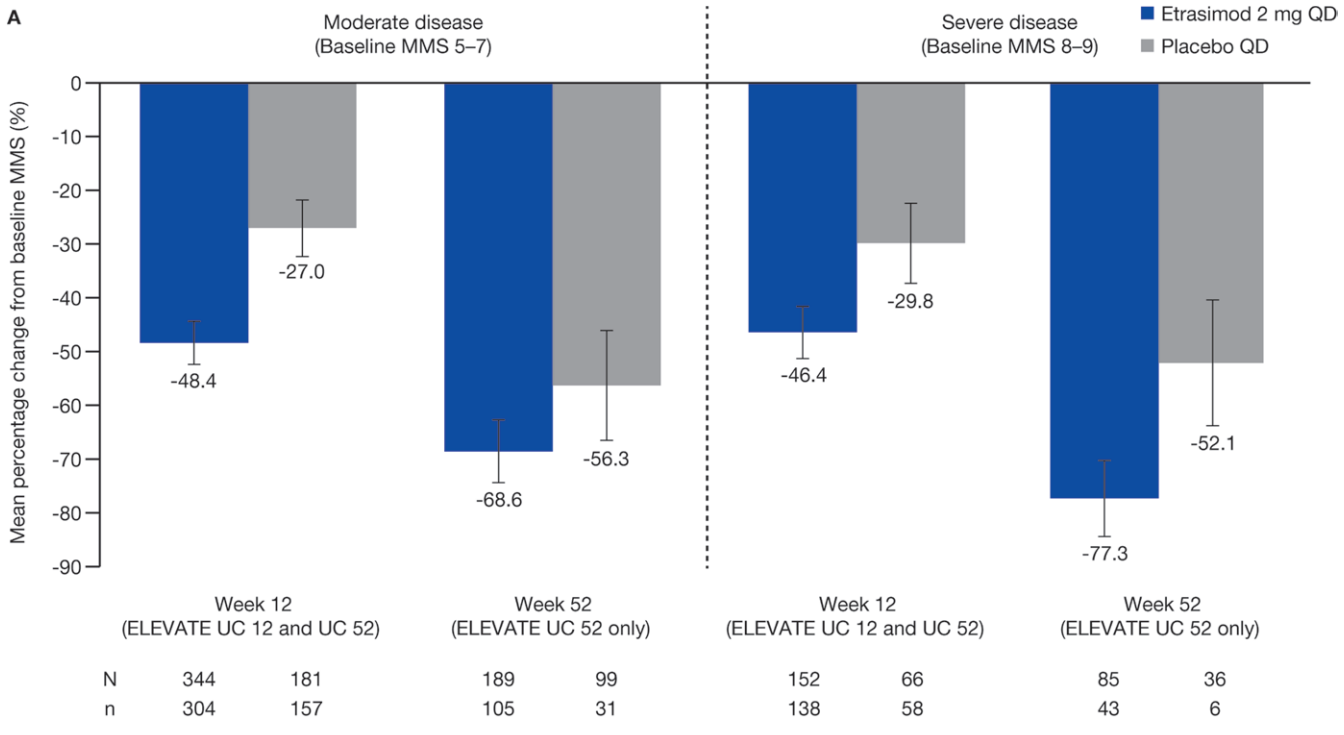
[a]Left-sided colitis and pancolitis were entered by investigators.
[b]Isolated proctitis was confirmed through a central read.
Abbreviations: 5-ASA, 5-aminosalicylates; CS, corticosteroid; ES, endoscopic subscore; JAKi, Janus kinase inhibitor; MMS, modified Mayo score; *N*, number of patients in the baseline disease activity subgroup by treatment; *n*, number of patients in the specified category; QD, once daily; RBS, rectal bleeding subscore; SD, standard deviation; SFS, stool frequency subscore; UC, ulcerative colitis.

placebo, respectively. For patients with severely active disease at baseline, 21.7% (95% CI, 14.4 to 31.4) and 10.6% (95% CI, 4.2 to 24.2) treated with etrasimod and placebo achieved an MMS of 0–2, respectively (Figure 2). A similar trend was observed at week 52, with 38.6% (95% CI, 30.0 to 48.0) of patients treated with etrasimod and 15.2% (95% CI, 8.1 to 26.6) of patients treated with placebo achieving an MMS of 0–2 in the moderately active disease at baseline subgroup vs 36.5% (95% CI, 24.5 to 50.4) of patients treated with etrasimod and 2.8% (95% CI, 0.3 to 19.9) of patients treated with placebo in the severely active disease at baseline subgroup (Table S4). We note that there were imbalances between baseline disease activity subgroups at week 52.

At week 12, higher proportions of patients who were biologic/JAKi-naïve achieved clinical remission with etrasimod vs placebo, in both baseline disease activity subgroups (MMS 5–7: 42.1% vs 19.8%; MMS 8–9: 25.5% vs 9.8% for etrasimod vs placebo, respectively) (Table S5). This was consistent for biologic/JAKi-experienced patients in the moderately active disease at baseline subgroup (29.8% for etrasimod vs 10.9% for placebo), although similar proportions of biologic/JAKi-experienced patients in the severely active disease at baseline subgroup achieved clinical remission in both treatment groups (14.0% for etrasimod vs 12.0% for placebo) (Table S5).

Safety

The proportions of patients with TEAEs were similar between etrasimod and placebo for both the moderately and severely active baseline disease subgroups (proportions of patients with any TEAE: moderately active [MMS: 5–7]: 59.0% vs 50.8%, severely active [MMS 8–9]: 65.1% vs 56.1% for etrasimod vs placebo, respectively; Table 4). Similar proportions of patients who had moderately active (5.8% and 3.3% for etrasimod and placebo, respectively) vs



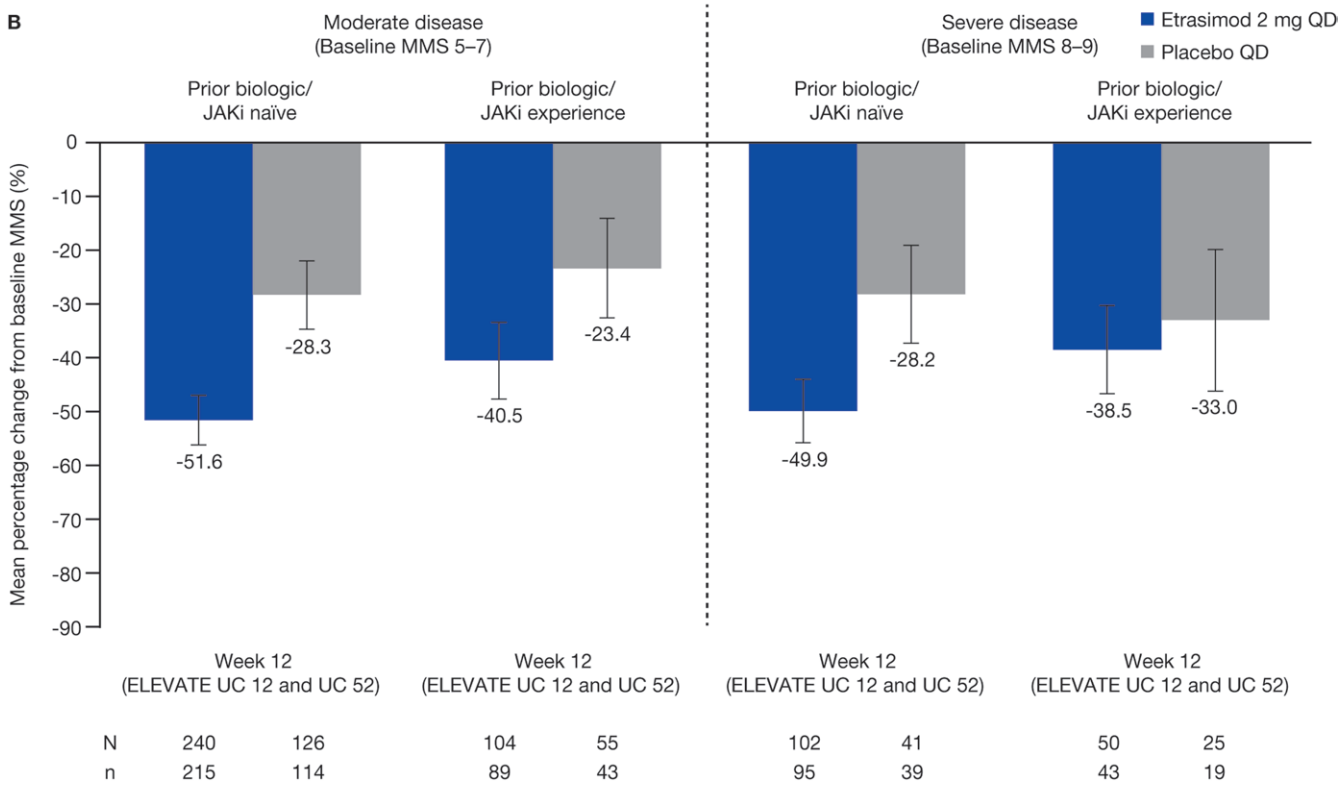


Figure 1. Mean percentage change (95% CI) in MMS (MMS 5–7; MMS 8–9) at week 12 and week 52 (A) and at week 12 in pooled data from both ELEVATE UC 52 AND ELEVATE UC 12 stratified by biologic/JAKi-experience subgroups according to baseline MMS (B) (FAS). Bars represent 95% CIs. Abbreviations: CI, confidence interval; FAS, full analysis set; JAKi, Janus kinase inhibitor; MMS, modified Mayo score; *N*, number of patients in the full analysis set at the specified time point; *n*, number of patients with observations at a visit; UC, ulcerative colitis.

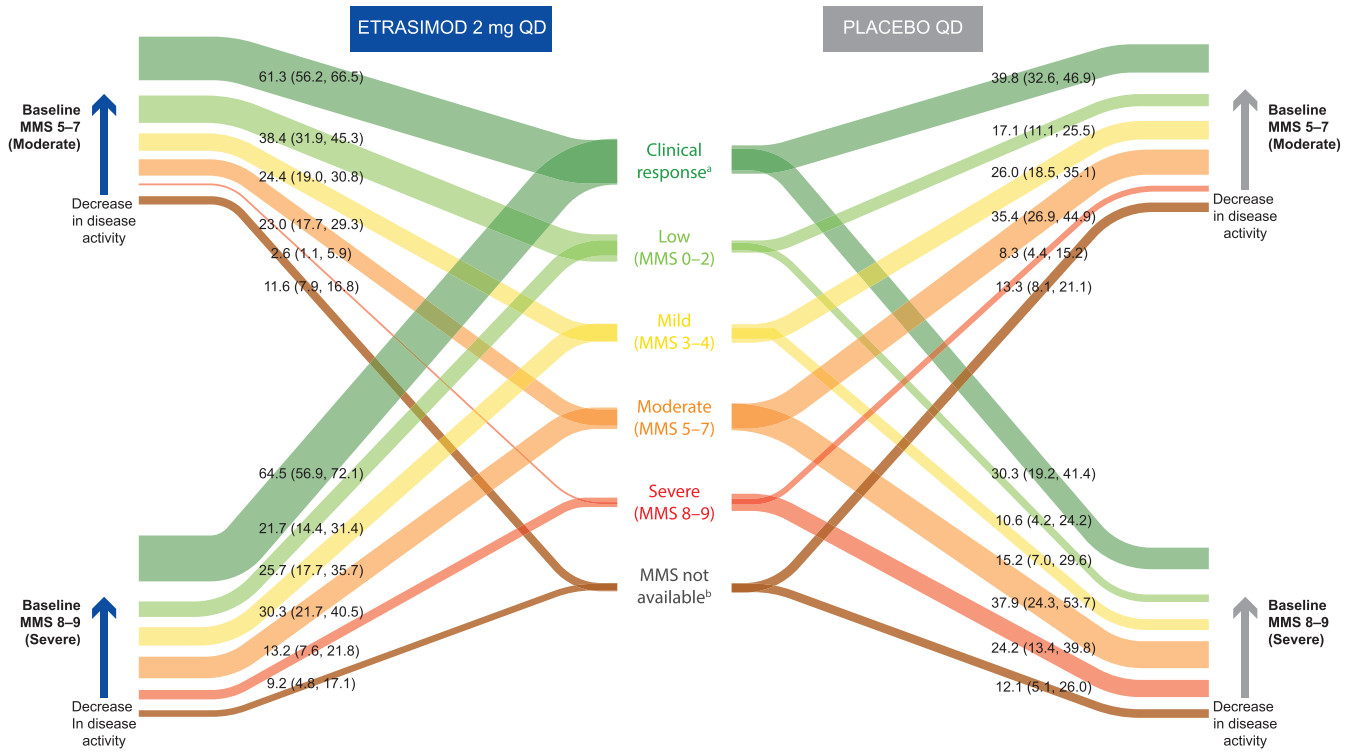


Figure 2. Proportion of patients achieving clinical response and each MMS category at week 12 stratified according to baseline disease activity (pooled data from ELEVATE UC 52 and ELEVATE UC 12). Lines extending from each corner are representative of each disease activity subgroup in this analysis. Patients with moderately active disease (MMS 5–7) at baseline are reflected in the lines extending from the top of the diagram with patients with severely active disease (MMS 8–9) at baseline reflected in the lines extending from the bottom of the diagram. The left and right sides represent patients treated with etrasimod and placebo, respectively. Line thickness reflects the proportions of patients who achieved clinical response (dark green line) and the proportions of patients with different levels of disease activity at week 12 (severe [red]—low [light green]; each arrow points to a decrease in disease activity). [a]Clinical response was defined as a ≥2-point and ≥30% decrease from baseline in MMS, and a ≥1-point decrease from baseline in RBS or RBS ≤ 1. [b]MMS was not available for some patients at week 12 for various reasons, including discontinuation prior to week 12. Abbreviations: MMS, modified Mayo score; RBS, rectal bleeding subscore; UC, ulcerative colitis.

severely active disease (3.3% and 3.0% for etrasimod and placebo, respectively) at baseline had a TEAE that led to treatment discontinuation across treatment groups (Table 4). Across disease activity subgroups, the proportions of patients with AEs of interest were low (Table 5). The most frequent AEs of interest were increased alanine aminotransferase (in ≤2.9% of patients) and hypertension (in ≤2.6% of patients; Table 5).

After medical review based upon specific AESI criteria, the following events (PT) were deemed AESI for the moderately active disease subgroup: Sinus bradycardia, *n* = 2 (etrasimod/MMS 5–7); bradycardia, *n* = 1 (etrasimod/MMS 5–7); herpes zoster, *n* = 2 (etrasimod/MMS 5–7), *n* = 2 (placebo/MMS 5–7); oral herpes, *n* = 2 (etrasimod/MMS 5–7); atrioventricular block first degree, *n* = 1 (etrasimod/MMS 5–7); atrioventricular block second degree, *n* = 1 (etrasimod/MMS 5–7); hypertension, *n* = 7 (etrasimod/MMS 5–7), *n* = 1 (placebo/MMS 5–7); essential hypertension, *n* = 1 (placebo/MMS 5–7). In the severely active disease subgroup, the following events were deemed AESI: bradycardia, *n* = 1 (etrasimod/MMS 8–9); herpes simplex, *n* = 1 (etrasimod/MMS 8–9); oral herpes, *n* = 1 (etrasimod/MMS 8–9), *n* = 1 (placebo/MMS 8–9); hypertension, *n* = 4 (etrasimod/MMS 8–9); blood pressure increased, *n* = 1 (etrasimod/MMS 8–9); hypertensive crisis, *n* = 1 (etrasimod/MMS 8–9); macular edema, *n* = 1 (etrasimod/MMS 8–9).

Discussion

In this post hoc analysis of the ELEVATE UC 52 and ELEVATE UC 12 trials, we demonstrated that treatment with etrasimod, compared with placebo, improved UC disease activity, regardless of whether patients had moderately (MMS 5–7) or severely (MMS 8–9) active disease at baseline. Moreover, we show that etrasimod had clinically meaningful treatment effects vs placebo in all subgroups, although the treatment effect was more consistent among prior biologic/JAKi-naïve vs -experienced patients. This effect was numerically smaller in patients with both prior advanced therapy experience and severely (MMS 8–9) active disease than in other subgroups. A higher proportion of patients who did not respond to etrasimod had an ES of 3 in the moderately active disease subgroup, indicating that patients with a higher baseline ES may be slower to respond to treatment.

Patients treated with etrasimod showed a larger percentage decrease in MMS at week 12 than patients treated with placebo, regardless of baseline MMS score. At week 12, more patients treated with etrasimod also achieved a clinical response compared with placebo in both disease activity subgroups. The proportions of patients who achieved a clinical response and were treated with etrasimod were similar between disease activity subgroups (61.3% and 64.5% for moderately active and severely active disease, respectively). Reflecting the clinical impact of severely active UC, a greater

Table 4. Summary of safety (most common TEAEs[a]) in the ELEVATE UC clinical program stratified according to baseline disease activity.

Patients, *n* (%) [IR per 100 PY]	ELEVATE UC 52 + ELEVATE UC 12 (pooled) Baseline MMS 5–7 (*N* = 525)		ELEVATE UC 52 + ELEVATE UC 12 (pooled) Baseline MMS 8–9 (*N* = 218)	
	Etrasimod 2 mg QD (*N*1 = 344)	Placebo QD (*N*1 = 181)	Etrasimod 2 mg QD (*N*1 = 152)	Placebo QD (*N*1 = 66)
Any TEAE	203 (59.0) [213.41]	92 (50.8) [208.26]	99 (65.1) [287.07]	37 (56.1) [271.26]
Any serious TEAE[b]	19 (5.5) [10.96]	7 (3.9) [9.69]	6 (3.9) [7.86]	4 (6.1) [17.96]
Any TEAE leading to discontinuation	20 (5.8) [11.24]	6 (3.3) [8.16]	5 (3.3) [6.56]	2 (3.0) [8.63]
SOC PT				
Gastrointestinal disorders	61 (17.7) [38.98]	29 (16.0) [44.33]	35 (23.0) [55.37]	15 (22.7) [73.80]
Colitis ulcerative	17 (4.9) [9.65]	8 (4.4) [11.04]	10 (6.6) [13.24]	6 (9.1) [26.93]
Infections and infestations	59 (17.2) [37.36]	33 (18.2) [53.90]	34 (22.4) [52.20]	10 (15.2) [49.88]
Investigations	45 (13.1) [28.19]	18 (9.9) [26.05]	17 (11.2) [23.53]	3 (4.5) [13.24]
Musculoskeletal and connective tissue disorder	36 (10.5) [22.17]	13 (7.2) [18.67]	15 (9.9) [21.01]	1 (1.5) [4.33]
Nervous system disorders	36 (10.5) [21.86]	10 (5.5) [14.12]	22 (14.5) [33.57]	8 (12.1) [36.42]
Headache	20 (5.8) [11.70]	5 (2.8) [6.91]	10 (6.6) [13.99]	3 (4.5) [13.19]
Dizziness	9 (2.6) [5.12]	0	8 (5.3) [10.92]	1 (1.5) [4.26]
Blood and lymphatic system disorders	30 (8.7) [17.42]	17 (9.4) [24.59]	19 (12.5) [28.06]	7 (10.6) [31.47]
Anemia	21 (6.1) [12.00]	15 (8.3) [21.65]	17 (11.2) [24.91]	6 (9.1) [26.89]
General disorders and administration-site conditions	25 (7.3) [14.77]	13 (7.2) [18.66]	15 (9.9) [20.73]	8 (12.1) [35.92]
Metabolism and nutrition disorders	25 (7.3) [14.54]	6 (3.3) [8.25]	9 (5.9) [12.31]	1 (1.5) [4.29]
Skin and subcutaneous tissue disorders	16 (4.7) [9.13]	9 (5.0) [12.81]	11 (7.2) [15.38]	7 (10.6) [33.44]
Eye disorders	16 (4.7) [9.18]	4 (2.2) [5.53]	8 (5.3) [10.66]	4 (6.1) [17.12]
Cardiac disorders	12 (3.5) [6.78]	4 (2.2) [5.46]	9 (5.9) [12.16]	0

[a]The most common TEAEs were defined as those that occurred in >5% of patients who received etrasimod or placebo across disease activity subgroups.
[b]Serious adverse events were defined as any events that resulted in death, were life threatening, required patient hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability or incapacity, resulted in a congenital anomaly or birth defect, or were deemed medically significant.
Abbreviations: IR, incidence rate; MMS, modified Mayo score; *N*, number of patients in each disease activity subgroup; *N*1, number of patients in each treatment group; *n*, number of patients experiencing each adverse event; PT, Preferred Term; PY, patient-year; QD, once daily; SOC, System Organ Class; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

proportion of patients who received placebo with moderately active vs severely active disease achieved a clinical response (39.8% vs 30.3%). These observations were still evident at week 52 (patients in ELEVATE UC 52 only).

As expected, the therapeutic goal of clinical remission reflected by an MMS of 0–2 (specifically, an SFS of 0 [or 1 with a ≥1-point decrease from baseline], RBS of 0, and ES of ≤1 [excluding friability]) was reached at week 12 by more patients who had moderately active vs severely active disease at trial baseline, with numerically higher responses seen for patients treated with etrasimod vs placebo in both disease severity subgroups. However, 21.7% of patients with severely active disease at baseline had mildly active disease (MMS 3–4) by week 12. Among those treated with etrasimod, at week 52, a marginally higher proportion with moderately active disease at baseline (38.6%) had an MMS of 0–2 compared to those patients with severely active disease at the start of the study (36.5%). This difference in the proportions of patients achieving an MMS of 0–2 between activity subgroups was smaller than expected, which may be reflective of a smaller sample size in the severely active disease subgroup at week 52. Overall, these findings are consistent with the efficacy of etrasimod vs placebo reported in the primary analysis of the ELEVATE UC clinical program.[12] Reductions in Mayo score and MMS from baseline to week 52 were seen with the S1P receptor modulator ozanimod, with week 52 scores remaining generally stable during an open-label extension study.[18] Data are unavailable with respect to treatment response with ozanimod when stratified according to patients' baseline disease activity.

Greater proportions of patients with moderately active disease than severely active disease at baseline achieved clinical remission, endoscopic improvement, and EIHR at week 12. The proportions of patients achieving these endpoints were numerically smaller than the proportion of patients achieving clinical response at week 12, which is consistent with the primary analysis of the ELEVATE UC clinical program.[12] This found that of patients treated with etrasimod in ELEVATE UC 52, 27% achieved clinical remission, 35% achieved endoscopic improvement, and 21% achieved EIHR at week 12, while 62% of patients achieved clinical response at week 12.[12]

Corresponding to the primary analyses of ELEVATE UC 52 and ELEVATE UC 12,[12] at week 12, patients with prior exposure to advanced treatments for UC (biologic/JAKi) had reduced efficacy vs patients naïve to advanced treatments as measured by mean percentage change in baseline MMS. The

Table 5. Adverse events of interest[a] in the ELEVATE UC clinical program stratified according to baseline disease activity.

	ELEVATE UC 52 + ELEVATE UC 12 (pooled) Baseline MMS 5–7 (*N* = 525)		ELEVATE UC 52 + ELEVATE UC 12 (pooled) Baseline MMS 8–9 (*N* = 218)	
n **(%) [IR/100 PY]**	**Etrasimod 2 mg QD (*N*1 = 344)**	**Placebo QD (*N*1 = 181)**	**Etrasimod 2 mg QD (*N*1 = 152)**	**Placebo QD (*N*1 = 66)**
Macular edema	1 (0.3) [0.56]	0	1 (0.7) [1.30]	1 (1.5) [4.26]
AV block first degree	1 (0.3) [0.56]	0	1 (0.7) [1.31]	0
AV block second degree[b]	1 (0.3) [0.56]	0	0	0
Bradycardia	3 (0.9) [1.68]	0	2 (1.3) [2.60]	0
Sinus bradycardia	3 (0.9) [1.67]	0	1 (0.7) [1.30]	0
Cytomegalovirus infection	0	0	1 (0.7) [1.30]	0
Tuberculosis	0	1 (0.6) [1.35]	0	0
Herpes zoster[c]	2 (0.6) [1.12]	2 (1.1) [2.71]	0	0
Hypertension	7 (2.0) [3.97]	2 (1.1) [2.72]	4 (2.6) [5.26]	0
Alanine aminotransferase increased	10 (2.9) [5.68]	1 (0.6) [1.35]	1 (0.7) [1.30]	0
Aspartate aminotransferase increased	4 (1.2) [2.25]	2 (1.1) [2.73]	1 (0.7) [1.30]	1 (1.5) [4.35]
Pulmonary function test decreased	1 (0.3) [0.56]	0	0	0
Forced expiratory volume decreased	0	0	1 (0.7) [1.30]	0
FEV_1/FVC ratio decreased	0	2 (1.1) [2.71]	0	0

[a]Adverse events of interest include the subset of AESIs which met sponsor-defined criteria.
[b]Mobitz type 1; no events of AV block second degree or higher were reported in any treatment group.[12]
[c]Per the protocol, the history of herpes zoster vaccination was not collected in the electronic case report form at study entry. Patients who experienced herpes zoster events did not report a history of herpes zoster vaccination during the study screening period.
Abbreviations: AESI, adverse event of special interest; AV, atrioventricular; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; IR, incidence rate; MMS, modified Mayo score; *N*, number of patients in each disease activity subgroup; *N*1, number of patients in each treatment group; *n*, number of patients with events within the risk period; PY, patient-year; QD, once daily; UC, ulcerative colitis.

mean percentage change in MMS from baseline was generally similar for patients with both moderately active and severely active disease in each treatment group, for each prior biologic/JAKi-experience subgroup. However, there was a minimal difference in percentage change in MMS between treatment groups for patients with prior experience with biologic/JAKi and severely active disease at baseline (~5%), although this may reflect the small number of patients in this subgroup.

Median levels of FCP and hsCRP were higher in patients with severely active vs moderately active disease at baseline. Our data suggest, diagnostically, that an FCP level of >1200 µg/g and hsCRP of > 5.0 mg/L may be indicative of patients with severely active disease (MMS 8–9). Moreover, at week 12, greater reductions in concentrations of FCP, but not hsCRP, were observed in patients treated with etrasimod who were clinical responders and had moderately active vs severely active disease at baseline, highlighting the role of this inflammatory biomarker as an objective measure of assessing inflammatory burden and disease activity.

The overall safety profile of etrasimod from ELEVATE UC 52 and ELEVATE UC 12 has previously been described in detail with a demonstrated favorable risk-benefit profile.[12] Although a slightly higher proportion of patients with moderately active compared to severely active disease discontinued treatment due to TEAE, this post hoc analysis demonstrated that the safety profile of etrasimod was broadly similar for patients with either moderately or severely active baseline UC.

Limitations of this study are the descriptive nature of the analysis and, as a post hoc study, the study population was not designed for these stratifications. This resulted in imbalances between subgroups and an insufficient sample size to enable treatment comparisons for efficacy analyses and subsequent data interpretation, preventing any further conclusions from being drawn. In particular, sample sizes were limited for patients with a baseline MMS 8–9 and treated with placebo and for subgroups assessed at week 52. Further research into these populations in a clinical trial or observational setting is needed to assess the generalizability of these data to the population of patients with moderately active and severely active UC.

Conclusions

In the ELEVATE UC 52 and ELEVATE UC 12 trials, treatment of patients with moderately to severely active UC with etrasimod led to greater reductions in disease activity and consistently higher rates of clinical response vs placebo, regardless of patients' baseline disease activity. Patients that were naïve to biologic/JAKi at baseline tended to experience a greater reduction in MMS than those with prior experience with biologic/JAKi, regardless of baseline disease activity. The safety profile of etrasimod was not impacted by baseline disease activity and was consistent with the overall ELEVATE UC population. Collectively, these results indicate that baseline disease activity does not impact the safety and efficacy of etrasimod in the treatment of patients with UC and substantiates the use of etrasimod across all subsets of patients with moderately to severely active UC.

Supplementary Data

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

Acknowledgments

The authors would like to thank the patients, investigators, and study teams who were involved in the etrasimod UC program. Medical writing support, under the direction of the authors, was provided by Adam Creasey, MSc, CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer, New York, NY, USA, in accordance with Good Publication Practice (GPP 2022) guidelines.[19]

Author Contributions

Concept and methodology: E.S., J.C.W., M.G., B.E.S., A.J.Y. Project administration: E.S., J.C.W., J.W. Supervision: E.S., J.C.W. Data curation: E.S., J.C.W. Investigation: E.S., J.C.W., M.G., J.W. Patient recruitment: B.E.S., M.C.D., O.G.J., S.V., R.P., M.D.L., A.J.Y. Data analysis: J.W., E.S. Validation: all authors. Formal analysis, writing, reviewing, and editing the manuscript: all authors.

Funding

This work was funded by Pfizer.

Conflicts of Interest

B.E.S. has received consulting fees from AbbVie, Abivax, Alimentiv, Amgen, Arena Pharmaceuticals, Artugen Therapeutics, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Boston Pharmaceuticals, Calibr, Celgene, Celltrion, ClostraBio, Equillium, Enthera, Evommune, Fresenius Kabi, Galapagos, Genentech (Roche), Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Index Pharmaceuticals, Innovation Pharmaceuticals, Inotrem, Janssen, Kaleido, Kallyope, Lilly, Merck, Morphic Therapeutics, MRM Health, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, Sun Pharma, Surrozen, Takeda, Target RWE, Teva, Theravance Biopharma, TLL Pharmaceutical, and Ventyx Biosciences; has received speaking fees from Abivax, Bristol Myers Squibb, Janssen, Lilly, Pfizer, and Takeda; has received research grants from Bristol Myers Squibb, Janssen, Pfizer, Takeda, and Theravance Biopharma; has stock options with Ventyx Biopharma; and has received other support from Bristol Myers Squibb, Lilly, Janssen, Pfizer, and Takeda. M.C.D. has received consulting fees from AbbVie, Abivax, Arena Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Genentech, Gilead Sciences, Janssen Pharmaceuticals, Merck, Pfizer, Prometheus Laboratories, Prometheus Biosciences, and Takeda; has received grant/research support from Janssen; has shareholder/royalties in Trellus Health; and has directorship/ownership interest in Trellus Health. P.G.K. has received consulting and speaker fees from AbbVie, Janssen, Pfizer, and Takeda; and has received grant/research support from Pfizer and Takeda. S.V. has received lecture/speaker fees from AbbVie, Dr. Falk Pharma, Ferring, Galapagos, Hospira, Janssen, MSD, Takeda, and Tillotts; has received consultancy/advisory fees from AbbVie, AbolerIS Pharma, Alimentiv, Arena, AstraZeneca, Avaxia, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, CVasThera, Dr Falk Pharma, Eli Lilly, Ferring, Galapagos, Genentech/Roche, Gilead, Hospira, IMIDomics, Janssen, Johnson and Johnson, Materia Prima, MiroBio, Morphic, MRM Health, MSD, Mundipharma, Pfizer, ProDigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance Biopharma, Tillotts Pharma AG, and Zealand Pharma; and has received grant/research support from AbbVie, Galapagos, Janssen, MSD, Pfizer, and Takeda. R.P. has received consultancy fees from Abbott, AbbVie, Abivax, Alimentiv (formerly Robarts), Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, JAMP Bio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pendopharm, Pfizer, Progenity, Prometheus Biosciences, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Shire, Sublimity Therapeutics, Takeda Pharmaceuticals, Theravance Biopharma, Trellus, Viatris, Ventyx, and UCB; and has received advisory board fees for AbbVie, Alimentiv (formerly Robarts), Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Ferring, Fresenius Kabi, Genentech, Gilead Sciences, GlaxoSmithKline, JAMP Bio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pfizer, Progenity, Protagonist Therapeutics, Roche, Sandoz, Shire, Sublimity Therapeutics, Takeda Pharmaceuticals, and Ventyx; and has received research support from AbbVie, Janssen, Takeda, and Pfizer. M.D.L. has received consultancy fees from AbbVie, Bristol Myers Squibb, Intercept, Janssen, Lilly, Pfizer, Prometheus, Roche, Takeda, and Target RWE; and has received research support from Lilly, Pfizer, and Takeda. J.C.W. is an employee and shareholder of Pfizer Inc. J.W. is an employee and shareholder of Pfizer Inc. A.M. is an employee and shareholder of Pfizer Ltd. M.G. is an employee and shareholder of Pfizer AG. E.B. is an employee and shareholder of Pfizer Inc. A.J.Y. has received consultancy fees from AbbVie, Arena, Bristol Myers Squibb, Pfizer, and Takeda; and has received lecture/speaker fees from Bristol Myers Squibb.

Data Availability

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

Ethical Considerations

Both trials were conducted in compliance with the Declaration of Helsinki and were approved by the Institutional Review Boards at each investigational center participating in the studies. All patients provided written informed consent. All authors had access to the study data, and reviewed and approved the final manuscript.

References

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis. *Lancet*. 2017;389(10080):1756-1770. doi:10.1016/S0140-6736(16)32126-2
2. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413. doi:10.14309/ajg.0000000000000152

3. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110(9):1324-1338. doi:10.1038/ajg.2015.233
4. Harbord M, Eliakim R, Bettenworth D, et al.; European Crohn's and Colitis Organisation [ECCO]. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. *J Crohns Colitis*. 2017;11(7):769-784. doi:10.1093/ecco-jcc/jjx009
5. Pabla BS, Schwartz DA. Assessing severity of disease in patients with ulcerative colitis. *Gastroenterol Clin North Am*. 2020;49(4):671-688. doi:10.1016/j.gtc.2020.08.003
6. Naegeli AN, Hunter T, Dong Y, et al. Full, partial, and modified permutations of the Mayo Score: characterizing clinical and patient-reported outcomes in ulcerative colitis patients. *Crohns Colitis 360*. 2021;3(1):otab007. doi:10.1093/crocol/otab007
7. U.S. Department of Health & Human Services. *Ulcerative colitis: clinical trial endpoints. Guidance for industry*. Accessed February 3, 2024. https://www.fda.gov/files/drugs/published/Ulcerative-Colitis--Clinical-Trial-Endpoints-Guidance-for-Industry.pdf
8. US Food and Drug Administration. Ulcerative colitis: developing drugs for treatment. Accessed February 3, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ulcerative-colitis-developing-drugs-treatment.
9. European Medicines Agency. Development of new medicinal products for the treatment of ulcerative colitis - scientific guideline. Accessed February 3, 2024. https://www.ema.europa.eu/en/development-new-medicinal-products-treatment-ulcerative-colitis-scientific-guideline
10. Hanžel J, D'Haens GR. Anti-interleukin-23 agents for the treatment of ulcerative colitis. *Expert Opin Biol Ther*. 2020;20(4):399-406. doi:10.1080/14712598.2020.1697227
11. Sandborn WJ, Su C, Panes J. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;377(5):496-497. doi:10.1056/NEJMc1707500
12. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. *Lancet*. 2023;401(10383):1159-1171. doi:10.1016/S0140-6736(23)00061-2
13. Sands BE, Sandborn WJ, Panaccione R, et al.; UNIFI Study Group. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019;381(13):1201-1214. doi:10.1056/NEJMoa1900750
14. Danese S, Fiorino G, Peyrin-Biroulet L. Positioning therapies in ulcerative colitis. *Clin Gastroenterol Hepatol*. 2020;18(6):1280-1290.e1. doi:10.1016/j.cgh.2020.01.017
15. Turner D, Ricciuto A, Lewis A, et al.; International Organization for the Study of IBD. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology*. 2021;160(5):1570-1583. doi:10.1053/j.gastro.2020.12.031
16. Sandborn WJ, D'Haens GR, Sands BE, et al. Tofacitinib for the treatment of ulcerative colitis: an integrated summary of up to 7.8 years of safety data from the global clinical programme. *J Crohns Colitis*. 2023;17(3):338-351. doi:10.1093/ecco-jcc/jjac141
17. May WL, Johnson WD. A SAS macro for constructing simultaneous confidence intervals for multinomial proportions. *Comput Methods Programs Biomed*. 1997;53(3):153-162. doi:10.1016/s0169-2607(97)01809-9
18. Danese S, Panaccione R, Abreu MT, et al. Efficacy and safety of approximately 3 years of continuous ozanimod in moderately to severely active ulcerative colitis: interim analysis of the True North open-label extension. *J Crohns Colitis*. 2024;18(2):264-274. doi:10.1093/ecco-jcc/jjad146
19. DeTora LM, Toroser D, Sykes A, et al. Good Publication Practice (GPP) guidelines for company-sponsored biomedical research: 2022 update. *Ann Intern Med*. 2022;175(9):1298-1304. doi:10.7326/M22-1460