

The efficacy and safety of etrasimod as a first-line advanced therapy for ulcerative colitis: prespecified and post hoc subgroup data from the ELEVATE UC clinical program

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Abstract

Background: Many patients show inadequate response or intolerance to conventional therapies for ulcerative colitis (UC), including 5-aminosalicylates (5-ASA), thiopurines, and corticosteroids (CS). Etrasimod is an oral, once daily (QD), selective sphingosine 1-phosphate (S1P) receptor modulator for the treatment of UC.

Objectives: We assessed efficacy and safety as a first-line advanced therapy following different scenarios of conventional treatment.

Design: In the phase III, multicenter, double-blind, placebo-controlled ELEVATE UC trials, eligible patients were randomized 2:1 to etrasimod 2 mg QD or placebo.

Methods: Subgroups of patients post-5-ASA failure (prespecified), post-5-ASA/CS (post hoc), and post-thiopurine/5-ASA/CS (post hoc) were assessed for clinical, endoscopic, and histologic endpoints. Safety was assessed throughout the trials.

Results: In ELEVATE UC 52, 74 patients (45 receiving etrasimod 2 mg QD and 29 receiving placebo) had prior failure of 5-ASA only. Among these patients, a greater proportion of those treated with etrasimod versus placebo met clinical, endoscopic, and histologic endpoints at week 12 and week 52 (all $p < 0.01$). In complementary analyses using data pooled from ELEVATE UC 52 and ELEVATE UC 12, among those exposed to 5-ASA/CS ($N = 197$), a greater proportion receiving etrasimod versus placebo met all clinical efficacy endpoints assessed at week 12 and week 52 (all $p < 0.001$). In those exposed to thiopurine/5-ASA/CS ($N = 104$), similar efficacy was observed with statistically significant differences at week 12 and numerical differences that did not reach statistical significance at week 52. Subgroup safety outcomes were similar to those in the overall population.

Conclusion: Etrasimod is an effective first-line advanced treatment option for patients with UC early in their treatment journey, after 5-ASA, thiopurine, or CS use.

Trial registration: ClinicalTrials.gov: NCT03945188, NCT03996369.

Keywords: advanced therapy, etrasimod, ulcerative colitis

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Introduction

Ulcerative colitis (UC) is an inflammatory disease characterized by progressive chronic inflammation of the inner lining of the large intestine.¹ This results in frequent bowel movements, rectal bleeding, bowel urgency, and pain, which lead to an impaired quality of life and increase the risk of long-term complications, including malignancy and the need for surgery.^{1,2}

Therapeutic management of UC should be directed by the extent of bowel involvement, activity, and risk factors for adverse prognosis.³ Current treatment guidelines recommend using a combination of clinical, endoscopic, and patient-reported endpoints for UC management. For the early induction and maintenance of remission in moderately active UC, guidelines recommend conventional therapy, beginning with 5-aminosalicylates (5-ASA),³⁻⁶ often in combination with oral corticosteroids (CS),³⁻⁵ and sometimes with thiopurines, although their use varies geographically. 5-ASA treatment is associated with low adherence in real-world settings⁷ and intolerance-related adverse events (AEs)⁸; thiopurines are slow-acting, not recommended for induction, and also carry substantial safety concerns,^{3,4} as do oral CS, which may be used to induce remission or provide prompt control of symptoms but are ineffective as maintenance therapy.³ Patients taking conventional therapies for UC are thus often suboptimally controlled, as demonstrated by high discontinuation rates, dose escalation and augmentation, prolonged CS use, surgery, and hospitalization.^{9,10}

For patients with moderately to severely active UC whose disease is not controlled by conventional therapy, current guidelines recommend the early use of advanced therapies, noting that delaying treatment with advanced therapies may be detrimental.^{3,5} Despite this positioning, biologics and Janus kinase inhibitors (JAKi) are often only prescribed to patients who have cycled through several types of conventional therapy.¹¹

Etrasimod is an oral, once daily (QD), selective sphingosine 1-phosphate (S1P) receptor modulator for the treatment of UC. The efficacy and safety of etrasimod in this population were demonstrated in a 12-week phase II induction study (OASIS),¹² a 12-week phase III induction study (ELEVATE UC 12),¹³ two 52-week phase III studies (ELEVATE UC 52 and ENLIGHT

UC),^{13,14} and two open-label, long-term extension studies (OASIS OLE and the ongoing ELEVATE UC OLE).¹⁵⁻¹⁷ In these clinical trials, patients enrolled included those naïve to advanced therapies and those who had experience of biologic or JAKi therapies. The greatest efficacy with etrasimod was shown in patients who were biologic/JAKi naïve.¹⁸

S1P receptor modulators are recommended in the American College of Gastroenterology and American Gastroenterological Association (AGA) clinical guidelines for patients with moderately to severely active UC, with etrasimod being listed as a “higher efficacy medication” for patients naïve to advanced therapies in the AGA guidelines.^{3,5} In this analysis of data from the ELEVATE UC 52 and ELEVATE UC 12 trials, we aimed to describe the efficacy and safety of etrasimod as a first-line advanced therapy for UC by assessing efficacy in the predefined subgroup of patients who had only failed 5-ASA prior to enrolling in the ELEVATE UC trials, and thus were receiving step-up to advanced therapy without having failed any other conventional therapy. Additionally, we performed a complementary post hoc analysis to further characterize efficacy in patients who were advanced therapy naïve. In this analysis, we used pooled data from the aforementioned studies to assess efficacy in patients with prior oral 5-ASA exposure regardless of previous or concurrent CS use (but who were thiopurine naïve), and with prior thiopurine exposure regardless of prior or concomitant 5-ASA or CS use.

Methods

Study design

The phase III ELEVATE UC 52 and ELEVATE UC 12 trials were multicenter, randomized, double-blind, placebo-controlled trials in patients with moderately to severely active UC. ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) were registered on May 8, 2019, and June 21, 2019, respectively. Trial protocols and statistical analysis plans are available on clinicaltrials.gov. Eligible patients were randomized 2:1 to receive either etrasimod 2 mg QD or a matching placebo. Both trials encompassed a 28-day screening period, followed by a 12-week initial treatment phase; the ELEVATE UC 52 trial comprised a subsequent 40-week maintenance treatment phase.

Patients and the public were not involved in the design, conduct, or reporting of ELEVATE UC 52 or ELEVATE UC 12. The reporting of these analyses conforms to the Consolidated Standards of Reporting Trials (CONSORT) 2025 statement,¹⁹ while the reporting of the primary data from the ELEVATE UC 52 and ELEVATE UC 12 trials conformed to the relevant CONSORT statement of the time.¹³

Patients

Eligible patients were aged 16–80 years and provided written informed consent or assent. Patients had a diagnosis of UC at least 3 months prior to screening confirmed by endoscopic and histologic evidence, with active UC verified by endoscopy showing rectal involvement of at least 10 cm. Moderately to severely active UC was defined by a modified Mayo score (MMS) of 4–9, including endoscopic subscore (ES) ≥ 2 and rectal bleeding subscore (RBS) ≥ 1 . Patients had an inadequate response to, loss of response to, or intolerance to at least one conventional therapy (oral 5-ASA, CS, or thiopurines) or biologic (anti-tumor necrosis factor alpha, anti-integrin, or anti-interleukin 12/23 antibodies) or JAKi. Patients receiving 5-ASA and/or CS at baseline continued on stable doses throughout the duration of the trial, with CS tapering recommended during maintenance treatment. Concomitant treatment with a thiopurine was not permitted per protocol; prior treatment had to be discontinued ≥ 2 weeks prior to randomization.

Comprehensive study design and inclusion and exclusion criteria have been described elsewhere.¹³

Subgroups

Subgroup definitions are detailed in Table 1. The post-5-ASA failure subgroup was a prespecified subgroup in the ELEVATE UC 52 and ELEVATE UC 12 trials, whereas the post-5-ASA/CS and post-thiopurine/5-ASA/CS subgroups were defined post hoc among patients who were biologic/JAKi naïve, for further granularity around the early lines of treatment. Data for post-5-ASA/CS and post-thiopurine/5-ASA/CS subgroups were analyzed as pooled from ELEVATE UC 52 and ELEVATE UC 12 for time points up to and including week 12; data for week 52 are from ELEVATE UC 52 only.

Efficacy assessments

Prespecified endpoints (those that were defined in the protocols prior to trial commencement) assessed in all subgroups were clinical remission (stool frequency subscore [SFS] = 0, or 1 with a ≥ 1 -point reduction from baseline, RBS = 0, and ES ≤ 1 [excluding friability]), endoscopic improvement (ES ≤ 1), symptomatic remission (SFS = 0, or 1 with a ≥ 1 -point reduction from baseline and RBS = 0), endoscopic improvement-histologic remission (EIHR; ES ≤ 1 accompanied by histological remission i.e., a Geboes Index score < 2.0), CS-free clinical remission (patients who achieved clinical remission at week 52 and had not been receiving CS for ≥ 12 weeks immediately prior to week 52), sustained clinical remission (the proportion of patients achieving clinical remission at both week 12 and week 52), symptomatic response (decrease from baseline $\geq 30\%$ in composite RBS and SFS), complete symptomatic remission (SFS = 0 and RBS = 0), RBS, and SFS.

Post hoc endpoints (those that were defined, investigated, and analyzed following trial completion) were endoscopic normalization-histologic remission (Geboes Index score < 2.0 and ES = 0), endoscopic normalization-histologic remission allowing eosinophils (Geboes Index score $\leq 2B.0$ and ES = 0), EIHR allowing eosinophils (Geboes Index score $\leq 2B.0$ and ES ≤ 1 [if 1, must exclude friability]), and disease clearance (Nancy Histological Index = 0, ES = 0, RBS = 0, and SFS = 0 or 1 [if 1, must have ≥ 1 -point decrease from baseline]).

Safety assessments

The incidence and severity of AEs were monitored throughout both studies. All AEs were coded using the Medical Dictionary for Regulatory Activities version 24.1. Incidence rates, calculated as the number of events divided by patient-years (PY) adjusted to per 100 PY, were reported per subgroup. PY were the sum of the patient's time from baseline to first AE episode or time in the trial if the patient was event-free.

Statistical analyses

Statistical analyses were performed using SAS software, version 9.4 or later (SAS Institute Inc., Cary, NC, USA). For binary endpoints, percentages were based on the number of patients in the subgroup in the analysis set. Difference (95% confidence interval)

Table 1. Subgroup definitions and patients in each subgroup.

Subgroup	Description	Definition	Trial	Placebo, QD, N	Etrasimod 2 mg QD, N
Post-5-ASA failure	Prespecified subgroup ^a ; Efficacy was assessed separately in ELEVATE UC 52 and ELEVATE UC 12	Inadequate response, loss of response, or intolerance to previous treatment with oral 5-ASA and did not have an inadequate response, loss of response, or intolerance to any other previous UC medication	ELEVATE UC 52	29	45
			ELEVATE UC 12	12	28
Post-5-ASA/CS	Post hoc subgroup ^b ; Efficacy was assessed in pooled data from ELEVATE UC 52 and ELEVATE UC 12 up to week 12 and from ELEVATE UC 52 only at week 52	Previously exposed to, or currently taking, 5-ASA and included regardless of their prior or concomitant CS use or failure. Naïve to biologic/JAKi therapy for UC and naïve to thiopurines	ELEVATE UC 52	38	81
			ELEVATE UC 12	24	54
Post-thiopurine/5-ASA/CS	Post hoc subgroup ^b ; Efficacy was assessed in pooled data from ELEVATE UC 52 and ELEVATE UC 12 up to week 12 and from ELEVATE UC 52 only at week 52	Previously exposed to a thiopurine and included regardless of prior or concomitant 5-ASA or CS use or failure. Naïve to biologic/JAKi therapy for UC	ELEVATE UC 52	18	38
			ELEVATE UC 12	17	31
^a Defined in the protocols prior to trial commencement and in the statistical analysis plan prior to database lock; endpoints were assessed in each trial separately.					
^b Defined, investigated, and analyzed following trial completion; endpoints were assessed in the pooled ELEVATE UC 52 and ELEVATE UC 12 population.					
5-ASA, 5-aminosalicylates; CS, corticosteroids; JAKi, Janus kinase inhibitor; N, number of patients in subgroup; UC, ulcerative colitis.					

and two-sided *p* value were based on the Cochran–Mantel–Haenszel method adjusting to reported randomization stratification of (1) baseline CS use and (2) baseline disease activity (MMS 4–6 or 7–9). Missing response was treated as nonresponse. For continuous endpoints, least squares (LS) means were reported with estimates from a mixed-effect model with repeated measures for change from baseline with a covariate for baseline score, and factors for baseline CS use (yes vs no), baseline disease activity (MMS 4–6 or 7–9), trial, treatment, visit, and treatment by visit interaction. For pooled analyses, data from ELEVATE UC 52 and ELEVATE UC 12 were pooled to increase

the precision of efficacy estimates in clinically relevant subgroups. Both trials were similarly designed, randomized, double-blind, placebo-controlled phase III trials evaluating the same dose of etrasimod, with aligned eligibility criteria, endpoints, and assessment schedules during the induction period. Pooling was limited to common time points in the induction period, while week 52 analyses were restricted to ELEVATE UC 52. Potential between-trial differences were addressed by including trial as a factor in the statistical models. No additional heterogeneity analyses were specified. Certain analyses were conducted post hoc and should be regarded as exploratory. These

analyses were not powered to detect statistically significant differences; all reported p values were nominal, and no adjustments for multiplicity were applied.

Results

Patients

In the ELEVATE UC 52 prespecified post-5-ASA failure subgroup, 45 patients were receiving etrasimod and 29 patients were receiving placebo. In the ELEVATE UC 12 post-5-ASA failure subgroup, 28 patients were receiving etrasimod and 12 patients were receiving placebo. Demographics and baseline characteristics are summarized in Table 2 (ELEVATE UC 52) and Supplemental Table 1 (ELEVATE UC 12). Notably, in patients in the post-5-ASA failure subgroup enrolled in ELEVATE UC 52, a numerically greater proportion of patients receiving placebo (65.5%) had baseline ES=3 compared with those receiving etrasimod (42.2%). Also, a sizable proportion of patients receiving etrasimod (57.8%) versus placebo (44.8%) had an MMS 4–6 (Table 2).

Demographics and baseline characteristics for the post-5-ASA/CS and post-thiopurine/5-ASA/CS post hoc subgroups are summarized in Supplemental Table 2.

A total of 197 patients were included in the post-5-ASA/CS subgroup; 81 patients received etrasimod and 38 patients received placebo in ELEVATE UC 52 (Figure 1); 54 patients received etrasimod, and 24 patients received placebo in ELEVATE UC 12 (Supplemental Figure 1). The post-thiopurine/5-ASA/CS subgroup comprised a total of 104 patients; 38 patients received etrasimod, and 18 patients received placebo in ELEVATE UC 52; 31 patients received etrasimod, and 17 patients received placebo in ELEVATE UC 12.

Efficacy

Among patients enrolled in ELEVATE UC 52 in the post-5-ASA failure subgroup, a significantly greater (all $p < 0.001$) proportion of patients receiving etrasimod compared with placebo met the criteria for the prespecified efficacy endpoints of clinical remission, endoscopic improvement, symptomatic remission, and EIHR at week 12 and week 52, as well as CS-free clinical remission

and sustained clinical remission at week 52 (Figure 2).

In ELEVATE UC 12, this subgroup included fewer patients, and similar trends were seen at week 12, but statistical significance was not observed (Supplemental Figure 2).

A significantly greater (all $p < 0.01$) proportion of patients receiving etrasimod compared with placebo in this subgroup also met all composite endoscopic and histologic endpoints at week 12 and week 52 in ELEVATE UC 52 (Figure 3). Similar results were also seen at week 12 in ELEVATE UC 12 (Supplemental Figure 3).

Among patients in the post-5-ASA/CS subgroup, a significantly greater (all $p < 0.001$) proportion receiving etrasimod versus placebo were in clinical remission and showed endoscopic improvement at week 12 (pooled ELEVATE UC 52 and ELEVATE UC 12) and week 52 (ELEVATE UC 52 only), and CS-free clinical remission and sustained clinical remission at week 52 (ELEVATE UC 52 only; Figure 4a).

In the post-thiopurine/5-ASA/CS subgroup, a significantly greater proportion of patients receiving etrasimod versus placebo achieved clinical remission and endoscopic improvement at week 12 (pooled ELEVATE UC 52 and ELEVATE UC 12); numerical differences were observed for most endpoints at week 52 (ELEVATE UC 52 only; Figure 4b).

In the post-5-ASA/CS subgroup, there were significant observed differences for etrasimod compared with placebo as early as week 2 in the proportion of patients achieving symptomatic response ($p < 0.01$; Figure 5).

Differences were seen from week 4 for symptomatic remission ($p < 0.001$), as well as for LS mean change from baseline in RBS ($p < 0.001$) and SFS ($p < 0.01$; Figure 5).

Among patients in the post-thiopurine/5-ASA/CS subgroup, significant observed differences for etrasimod compared with placebo were seen at week 8 for symptomatic response ($p < 0.05$) and week 12 for symptomatic remission ($p < 0.01$). There were statistical differences in LS mean change from baseline in SFS from week 4 ($p < 0.01$; Figure 5).

Table 2. Demographics and baseline characteristics of patients in the prespecified post-5-ASA failure subgroup in ELEVATE UC 52 (FAS with MMS 4–9).

Demographic/baseline characteristic	Post-5-ASA failure	
	Placebo QD (N=29)	Etrasimod 2 mg QD (N=45)
Age (years), mean (SD)	43.0 (16.8)	36.4 (11.5)
Female sex, n (%)	12 (41.4)	22 (48.9)
BMI, mean (SD)	27.1 (6.1)	25.8 (5.4)
MMS, mean (SD)	6.6 (1.1)	6.2 (1.3)
MMS 4–6, n (%)	13 (44.8)	26 (57.8)
MMS 7–9, n (%)	16 (55.2)	19 (42.2)
ES=3, n (%)	19 (65.5)	19 (42.2)
fCAL (mg/kg), median (min, max)	1416.6 (49.8, 30831.4)	677.6 (12.1, 11172.1)
UC duration since diagnosis (years), mean (SD)	4.1 (4.3)	4.6 (5.6)
Baseline oral 5-ASA use: yes, n (%)	22 (75.9)	36 (80.0)
Baseline 5-ASA daily dose ^a (g/day)		
Median (min, max)	2.5 (0.4, 4.8)	2.0 (0.4, 9.6)
Mean (SD)	2.4 (1.3)	2.9 (2.1)
Biologic/JAKi naïve: yes, n (%)	28 (96.6) ^b	45 (100.0)
Baseline CS use: yes, n (%)	3 (10.3)	8 (17.8)
No prior TNFi or vedolizumab failure, n (%)	29 (100.0)	45 (100.0)
Disease extent		
Left-sided colitis, n (%)	24 (82.8)	28 (62.2)
Pancolitis, n (%)	5 (17.2)	10 (22.2)
Proctitis, n (%)	0	5 (11.1)

^aMesalamine/mesalamine equivalent.^bTwenty-eight of twenty-nine patients were biologic/JAKi naïve: in this group 0% had failed a TNFi or vedolizumab. One patient had previously taken vedolizumab, which was discontinued (not indicated as failed) due to pregnancy. As such, this patient was included in the post-5-ASA failure subgroup.

5-ASA, 5-aminosalicylates; BMI, body mass index; CS, corticosteroids; ES, endoscopic subscore; FAS, full analysis set; fCAL, fecal calprotectin; JAKi, Janus kinase inhibitor; MMS, modified Mayo score; N, number of patients in subgroup; n, number of patients with characteristic; QD, once daily; SD, standard deviation; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.

Safety

Safety in the post-5-ASA failure subgroup is summarized in Table 3, and was in line with safety in the overall ELEVATE UC population.¹³ There were five patients (6.8%) with six serious AEs in the etrasimod 2 mg group (each $n=1$; 1.4%); abdominal pain, colitis ulcerative,

proctitis, coronavirus [COVID]-19 pneumonia, elevated hepatic enzyme levels, and pregnancy with anembryonic gestation) and one (2.4%) patient receiving placebo (colitis ulcerative). The patient with elevated hepatic enzyme levels did not meet Hy's Law criteria for elevated hepatic enzymes or bilirubin, as previously reported.¹³

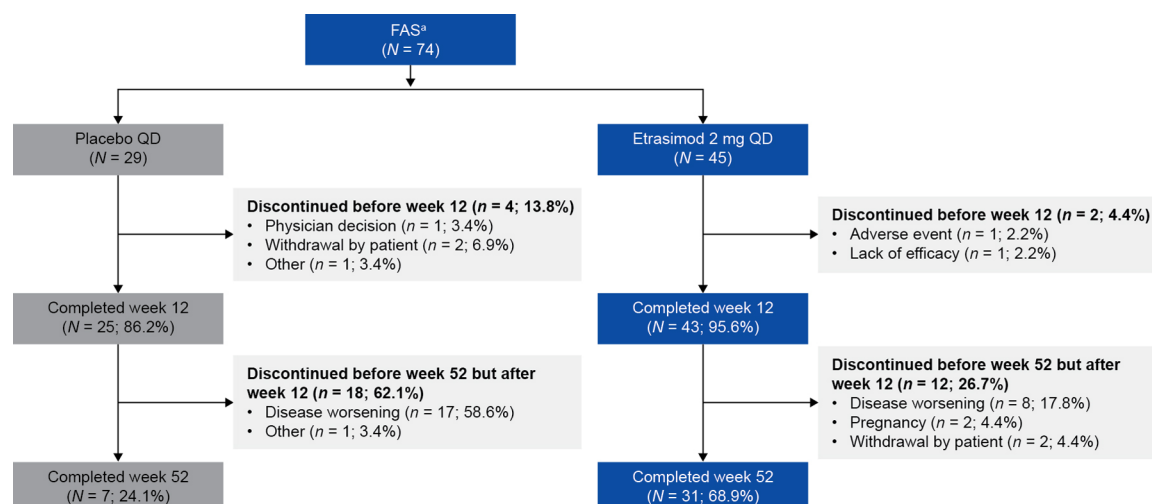


Figure 1. Patient disposition in the prespecified post-5-ASA failure subgroup in ELEVATE UC 52.

^aThe FAS comprised all patients receiving at least one dose of study treatment.

5-ASA, 5-aminosalicylates; FAS, full analysis set; N, number of patients in subgroup; n, number of patients with characteristic; QD, once daily; UC, ulcerative colitis.

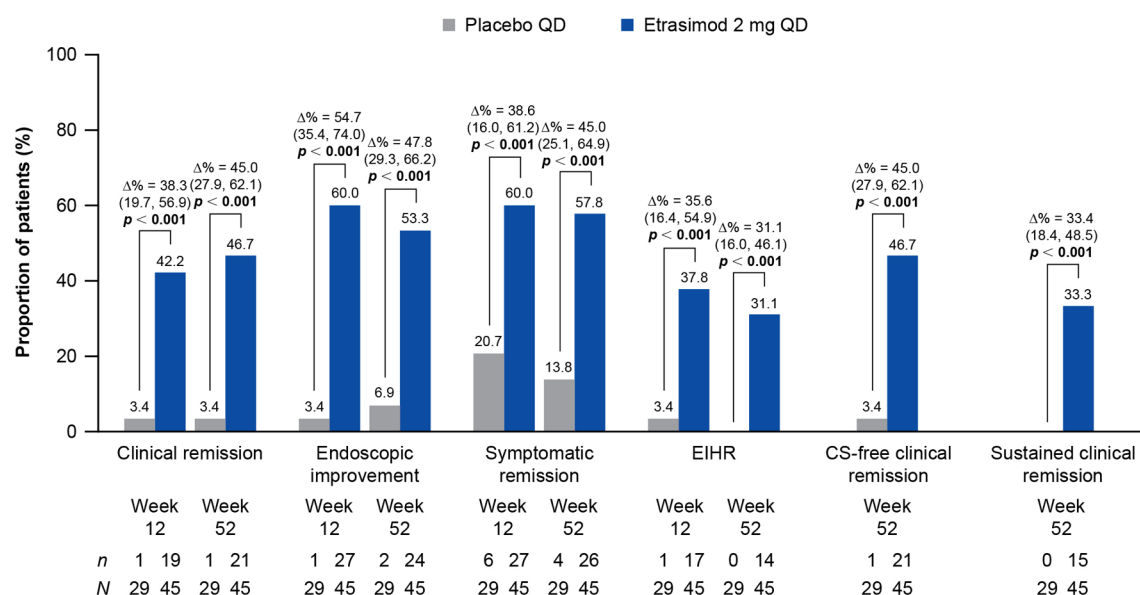


Figure 2. Proportion of patients in the prespecified post-5-ASA failure subgroup achieving predefined endpoints in ELEVATE UC 52 (FAS with MMS 4–9).

Values in brackets represent 95% CI. *p* values are two-sided *p* values to test the hypothesis of the risk difference being 0. Δ, adjusted treatment difference; 5-ASA, 5-aminosalicylates; CI, confidence interval; CS, corticosteroids; EIHR, endoscopic improvement-histologic remission; FAS, full analysis set; MMS, modified Mayo score; N, number of patients in subgroup; n, number of patients with endpoint; QD, once daily; UC, ulcerative colitis.

The patient with a pregnancy with anembryonic gestation, as previously described,²⁰ had an estimated pregnancy duration of exposure to etrasimod of 36 days. The patient had also

received umifenovir, which is contraindicated in pregnancy, for a respiratory tract infection. The outcome of the event was a medical termination.

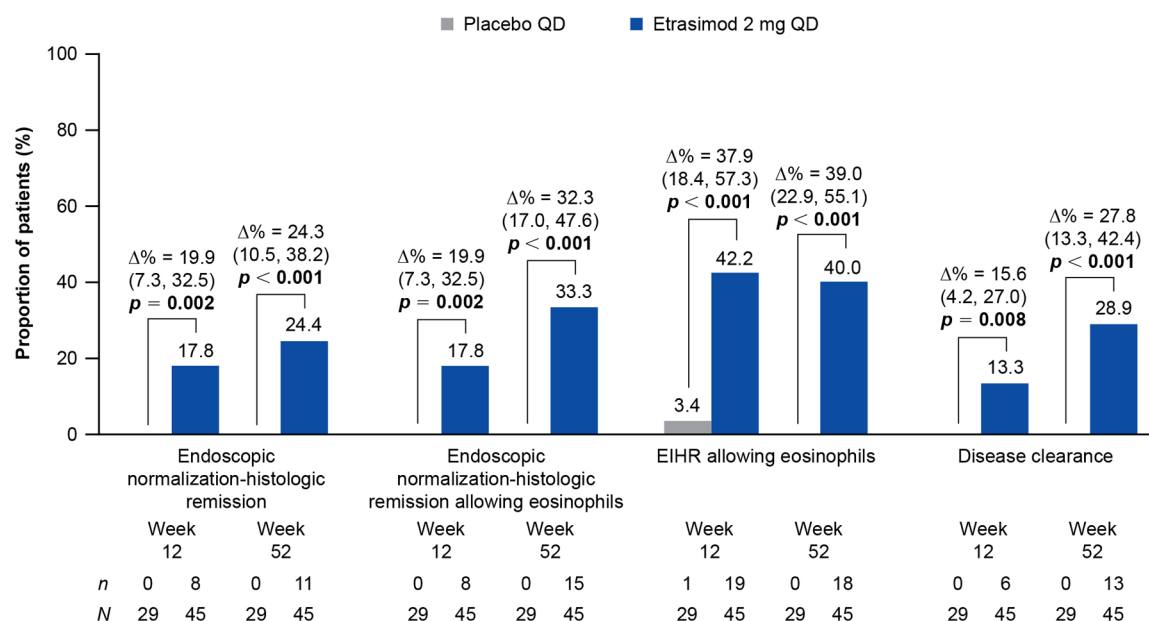


Figure 3. Proportion of patients in the prespecified post-5-ASA failure subgroup achieving composite endoscopic and histologic endpoints at week 12 and week 52 in ELEVATE UC 52 (FAS with MMS 4–9). Values in brackets represent 95% CI. *p* values are two-sided *p* values to test the hypothesis of the risk difference being 0. Δ , adjusted treatment difference; 5-ASA, 5-aminosalicylates; CI, confidence interval; EIHR, endoscopic improvement-histologic remission; FAS, full analysis set; MMS, modified Mayo score; *N*, number of patients in subgroup; *n*, number of patients with endpoint; QD, once daily; UC, ulcerative colitis.

AEs leading to study treatment discontinuation were reported in four patients (5.5%) receiving etrasimod 2 mg ($n=1$ [1.4%] each of first-degree atrioventricular [AV] block [on day 1 of treatment], colitis ulcerative, pyrexia, and blood alkaline phosphatase increased) and one patient (2.4%) receiving placebo (colitis ulcerative). The patient with the reported AE of AV block had preexisting AV block reported as an AE before the first dose of study drug that did not change 4 h after the dose, as previously described¹³; no additional AEs were reported for this patient.

Discussion

This analysis shows that etrasimod is effective in patients with UC who are early in their treatment journey and who, in line with multiple treatment guidelines,^{4,5} undergo direct escalation to advanced therapy treatment following 5-ASA treatment failure or inadequate response. In patients enrolled in ELEVATE UC 52 who were in the prespecified post-5-ASA failure subgroup, more than 40% of patients receiving etrasimod were in clinical remission after 12 weeks and, furthermore, not taking CS and in clinical remission at

52 weeks of treatment (significantly higher compared with just over 3% of patients taking placebo). In addition, more than 50% of patients had endoscopic improvement (an ES of 0 or 1), a significantly higher proportion compared with placebo. In post hoc analyses of pooled ELEVATE UC 52 and ELEVATE UC 12 data, we show efficacy in patients treated with other conventional therapies, CS and thiopurines.

Our data further demonstrate consistent results across multiple stringent endoscopic and histologic composite endpoints assessed in the ELEVATE UC 52 and ELEVATE UC 12 trials, which reflect treatment goals of deep remission. Although not yet identified as preferred targets for treatment of UC,³ achievement of histologic endpoints is considered an aspirational therapeutic goal in the STRIDE II guidelines.⁶ While it is considered a challenging target, achieving histologic endpoints is associated with improved clinical outcomes,²¹ lower rates of relapse, and fewer long-term complications.^{6,22}

The role of eosinophils in the pathogenesis of UC has not yet been fully elucidated; several studies

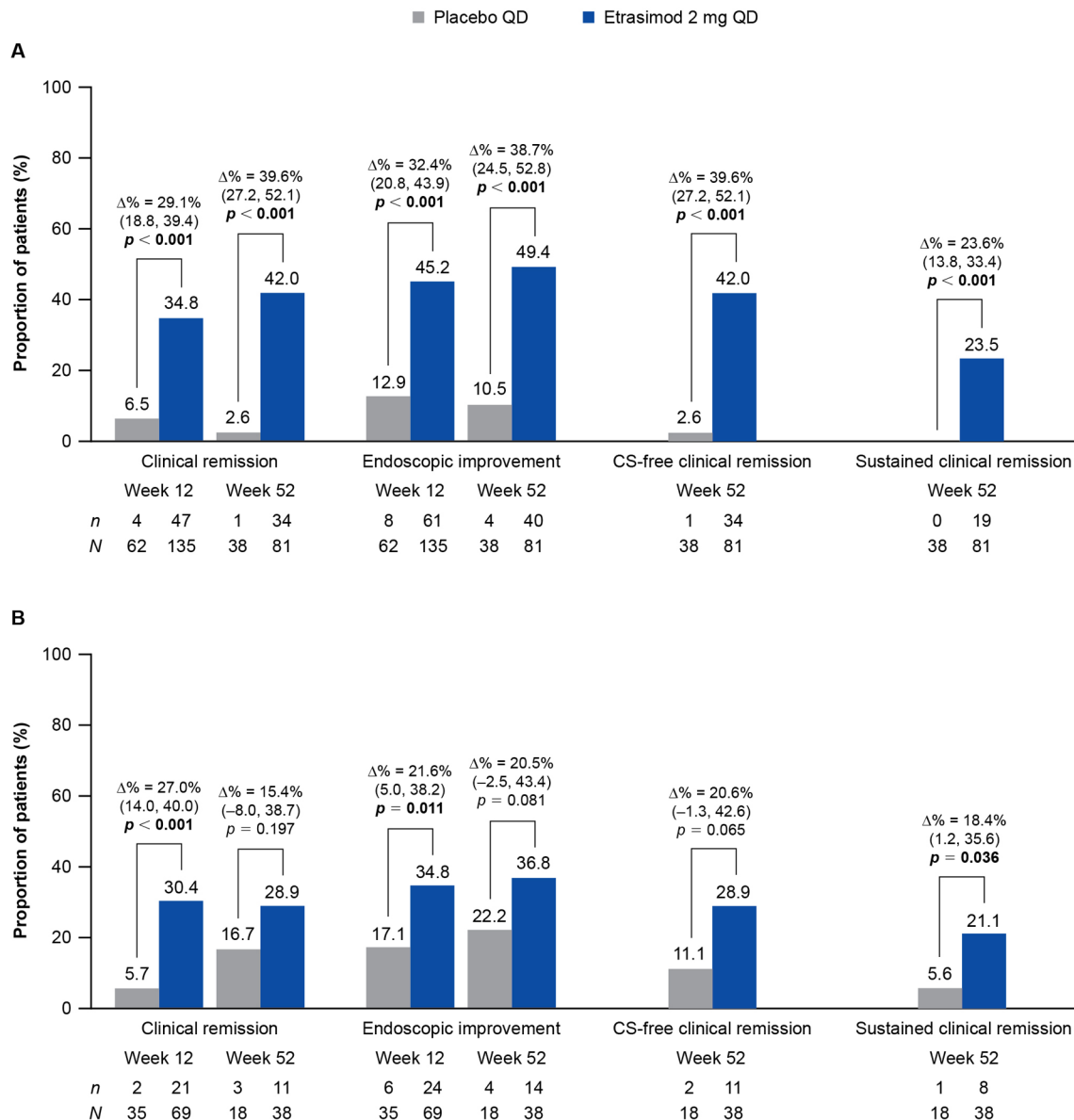


Figure 4. Proportion of patients achieving efficacy endpoints among patients in the post hoc (a) post-5-ASA/CS and (b) post-thiopurine/5-ASA/CS subgroups at week 12 (pooled ELEVATE UC 52 and ELEVATE UC 12) and week 52 (ELEVATE UC 52 only; FAS with MMS 4–9).

Values in brackets represent 95% CI. *p* values are two-sided *p* values to test the hypothesis of the risk difference being 0. Δ, adjusted treatment difference; 5-ASA, 5-aminosalicylates; CI, confidence interval; CS, corticosteroids; FAS, full analysis set; MMS, modified Mayo score; *N*, number of patients in subgroup; *n*, number of patients; QD, once daily; UC, ulcerative colitis.

associate eosinophils with higher disease activity, while others show a negative, or no, correlation.²³ Eosinophils are not part of the validated histologic endpoints; we therefore aimed to understand whether the inclusion of eosinophils in the lamina propria impacted the proportion of patients achieving EIHR or endoscopic

normalization-histologic remission endpoints. We saw a slightly higher proportion of patients achieving EIHR allowing eosinophils versus predefined EIHR (similarly for endoscopic normalization-histologic remission at week 52), for patients treated with etrasimod. Further research is required to understand this finding.

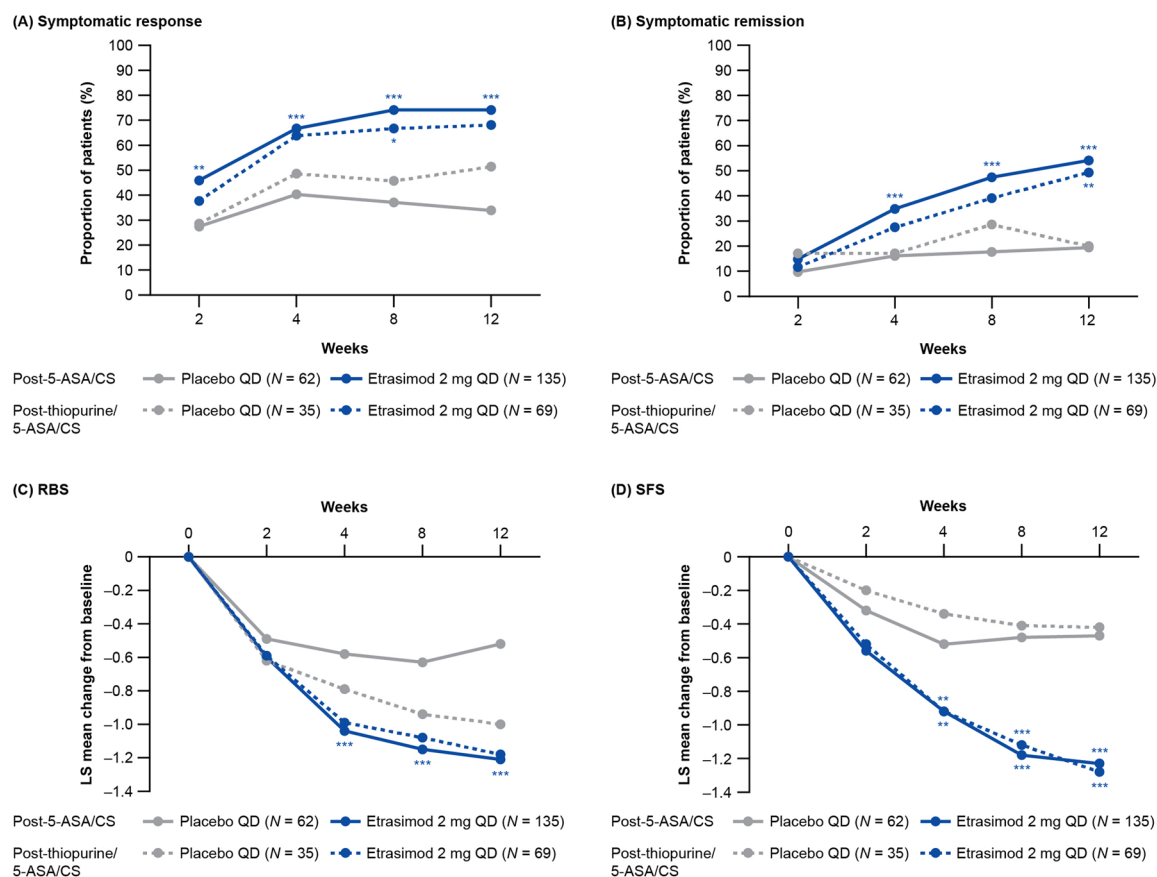


Figure 5. Proportion of patients achieving (a) symptomatic response and (b) symptomatic remission, as well as LS mean change from baseline in (c) RBS and (d) SFS, within the post hoc post-5-ASA/CS and post-thiopurine/5-ASA/CS subgroups in ELEVATE UC 52 and ELEVATE UC 12 [pooled data; FAS with MMS 4–9]. *p* values are two-sided *p* values to test the hypothesis of the risk difference being 0. 5-ASA, 5-aminosalicylates; CS, corticosteroids; FAS, full analysis set; LS, least squares; MMS, modified Mayo score; *N*, number of patients in group; QD, once daily; RBS, rectal bleeding subscore; SFS, stool frequency subscore; UC, ulcerative colitis. **p* < 0.05. ***p* < 0.01. ****p* < 0.001.

Table 3. AEs reported by patients in the post-5-ASA failure subgroup (pooled ELEVATE UC 52 and ELEVATE UC 12; safety analysis set).

<i>n</i> (%) [IR per 100 PY]	Post-5-ASA failure	
	Placebo QD, <i>N</i> = 41	Etrasimod 2 mg QD, <i>N</i> = 73
Any AE	18 (43.9) [153.5]	39 (53.4) [169.5]
Any serious AE	1 (2.4) [6.3]	5 (6.8) [11.7]
Any AE leading to discontinuation	1 (2.4) [6.2]	4 (5.5) [9.1]
Any infection	6 (14.6) [41.3]	13 (17.8) [33.6]
Any serious infection	0	1 (1.4) [2.3]

5-ASA, 5-aminosalicylates; AE, adverse event; IR, exposure-adjusted incidence rate; *N*, number of patients in subgroup; *n*, number of patients; PY, patient-years; QD, once daily; UC, ulcerative colitis.

Patients who received etrasimod in the post-5-ASA failure subgroup had a shorter disease duration (4.6 and 4.9 years in ELEVATE UC 52 and ELEVATE UC 12, respectively) compared with those receiving etrasimod in the overall ELEVATE UC trial populations (7.5 and 7.3 years, respectively).¹³ In addition, a sizable proportion of patients in the post-5-ASA failure subgroup in each trial had lower disease activity (defined as an MMS of 4–6) compared with the overall ELEVATE UC 52 and ELEVATE UC 12 trial populations (58% and 54%, respectively). These differences in baseline characteristics, which are known to be associated with better prognosis, are potential confounders in our analysis. While our data align with an analysis from the ELEVATE UC clinical program where the efficacy of etrasimod was demonstrated in patients with milder disease activity, as defined by an MMS 4–6,^{24,25} there are differences with regards to week 52 clinical remission rates observed in the phase II GLADIATOR trial, conducted in patients with mildly to moderately active UC (defined by an MMS 4–6, ES $\geq$ 2, and RBS $\geq$ 1). The primary endpoint of clinical remission at week 52 was not met in GLADIATOR, although significant differences from placebo were noted in other endpoints, especially at week 12.²⁵ In the GLADIATOR population, however, around a quarter of patients had biologic/JAKi experience, despite having mild to moderate disease activity.

An estimated 60% of patients with UC receive 5-ASA monotherapy as their initial treatment.²⁶ These patients typically further cycle through conventional therapies, receiving a mean of 6.3 courses of CS and 2.1 therapies with differing mechanisms of action (with almost 25% receiving three differing mechanisms of action) prior to escalation to an advanced therapy.¹¹ Physicians are often over-reliant on CS, prescribing them for more than 4 months per year in some cases despite concerns from patients regarding AEs.¹⁰ Almost half of patients receiving conventional therapies for their UC are dissatisfied with their treatments,²⁷ and many have indicators of suboptimal treatment, including symptom relapses, intolerance, and CS dependence, and therefore should be considered candidates for escalation to advanced therapy.²⁸

Several potential reasons exist for patients not being escalated to advanced therapies, including patients' low treatment expectations²⁹ and physician knowledge gaps in certain treatment

options,³⁰ including in steroid avoidance strategies. There is also ambiguity in defining treatment failure and the appropriate time for escalation, and both patients and physicians may express concerns regarding parenteral administration routes, potential AEs, and logistical considerations, which may result in hesitation to initiate advanced therapies.³¹ Additional barriers include uncertainty regarding the benefit of early escalation,³² access difficulty, insurance denial, and adequate site facilities for treatments requiring intravenous infusions.³³ There is thus a need for education around the benefits of earlier escalation to advanced therapy options among patients with UC, minimization and avoidance of steroid use, and the risks of failing to escalate those who are candidates for these treatments.

Our data have limitations, including that many of these are subgroup analyses with a limited number of patients. Analyses were not powered to detect statistically significant differences, and no adjustments were made for multiple comparisons. Some analyses were conducted post hoc and were exploratory in nature, and thus should be interpreted with caution. Findings are subject to the likelihood of false-positive results, potential confounding, and selection bias. Furthermore, the design of the ELEVATE UC trials does not allow etrasimod to be assessed in the context of any topical rectal therapies, which in clinical practice would likely be used in this patient population prior to escalation to advanced therapy. Treatment with topical rectal 5-ASA or rectal CS $\leq$ 2 weeks prior to or during screening was an exclusion criterion, and any use during the trials was not permitted. Despite these limitations, while most recent advanced therapies investigate efficacy in patients who are advanced therapy naïve versus experienced, our analysis is the first to demonstrate efficacy in a more granular patient population who are naïve to advanced therapy and reflects different treatment scenarios in which patients have only received conventional therapies.

Conclusion

Etrasimod was effective as a first-line advanced therapy for the treatment of UC, regardless of prior 5-ASA, thiopurine, or CS exposure, in both prespecified and exploratory subgroup analyses. Furthermore, etrasimod had a favorable safety profile in the post-5-ASA failure subgroup, consistent with safety described in the overall

population of the ELEVATE UC trials.¹³ Etrasimod thus provides an early advanced treatment option for advanced therapy candidates following conventional therapy failure. Expanded adoption of etrasimod use in this patient population is an opportunity to induce endoscopic and histologic remission in those earlier in their treatment journey. Our findings establish the need for prospective research into the use of advanced therapies in patients with UC who are early in their treatment journey.

Declarations

Ethics approval and consent to participate

ELEVATE UC 52 and ELEVATE UC 12 protocols were approved by the institutional review board at each participating center. Both trials were conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent to participate.

Consent for publication

All patients provided written informed consent.

Author contributions

David T. Rubin: Investigation; Writing – review & editing.

Charlie W. Lees: Investigation; Writing – review & editing.

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Karolina Wosik: Conceptualization; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

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.

Supplemental material

Supplemental material for this article is available online.

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