Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies

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Summary

Background Etrasimod, a once-daily, oral, sphingosine 1-phosphate (S1P) receptor modulator that selectively activates S1P receptor subtypes 1, 4, and 5, with no detectable activity on $S1P_{2,3}$, is in development for the treatment of immune-mediated diseases, including ulcerative colitis. In these two phase 3 trials, we aimed to evaluate the safety and efficacy of etrasimod in adult patients with moderately to severely active ulcerative colitis.

Methods In two independent randomised, multicentre, double-blind, placebo-controlled, phase 3 trials, ELEVATE UC 52 and ELEVATE UC 12, adults with active moderate-to-severe ulcerative colitis and an inadequate or loss of response or intolerance to at least one approved ulcerative colitis therapy were randomly assigned (2:1) to once-daily oral etrasimod 2 mg or placebo. Patients in ELEVATE UC 52 were enrolled from 315 centres in 40 countries. Patients in ELEVATE UC 12 were enrolled from 407 centres in 37 countries. Randomisation was stratified by previous exposure to biologicals or Janus kinase inhibitor therapy (yes *vs* no), baseline corticosteroid use (yes *vs* no), and baseline disease activity (modified Mayo score [MMS]; 4–6 *vs* 7–9). ELEVATE UC 52 comprised a 12-week induction period followed by a 40-week maintenance period with a treat-through design. ELEVATE UC 12 independently assessed induction at week 12. The primary efficacy endpoints were the proportion of patients with clinical remission at weeks 12 and 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12. Safety was evaluated in both trials. ELEVATE UC 52 and ELEVATE UC 12 were registered with ClinicalTrials.gov, NCT03945188 and NCT03996369, respectively.

Findings Patients in ELEVATE UC 52 were enrolled between June 13, 2019, and Jan 28, 2021. Patients in ELEVATE UC 12 were enrolled between Sept 15, 2020, and Aug 12, 2021. ELEVATE UC 52 and ELEVATE UC 12 screened 821 patients and 606 patients, respectively, with 433 and 354 subsequently undergoing random assignment. The full analysis set of ELEVATE UC 52 comprised 289 patients assigned to etrasimod and 144 to placebo. In ELEVATE UC 12, 238 patients were assigned to etrasimod and 116 to placebo. In ELEVATE UC 52, a significantly greater proportion of patients in the etrasimod group achieved clinical remission compared with patients in the placebo group at completion of the 12-week induction period (74 [27%] of 274 patients *vs* ten [7%] of 135 patients; p<0·0001) and at week 52 (88 [32%] of 274 patients *vs* nine [7%] of 135 patients; p<0·0001). In ELEVATE UC 12, 55 (25%) of 222 patients in the etrasimod group had clinical remission compared with 17 (15%) of 112 patients in the placebo group at the end of the 12-week induction period (p=0·026). Adverse events were reported in 206 (71%) of 289 patients in the etrasimod group and 81 (56%) of 144 patients in the placebo group in ELEVATE UC 52 and 112 (47%) of 238 patients in the etrasimod group and 54 (47%) of 116 patients in the placebo group in ELEVATE UC 12. No deaths or malignancies were reported.

Interpretation Etrasimod was effective and well tolerated as an induction and maintenance therapy in patients with moderately to severely active ulcerative colitis. Etrasimod is a treatment option with a unique combination of attributes that might address the persistent unmet needs of patients with ulcerative colitis.

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Introduction

Ulcerative colitis is a chronic, immune-mediated disease that is characterised by diffuse mucosal inflammation.[1] The goals of ulcerative colitis treatment are to achieve symptomatic control and to improve the endoscopic appearance of the mucosa.[2] Despite numerous approved treatments, many patients do not respond to therapy, or show a reduced response over time.[3] Additionally, many treatments require chronic parenteral administration or are associated with serious infections and malignancies.[4] Therefore, there is a need for safe and effective orally administrated ulcerative colitis treatment options. Although the cause of inflammatory bowel disease has not been fully elucidated, elevated levels of inflammatory

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Research in context

Evidence before this study

Etrasimod is an oral, once-daily, selective, sphingosine 1-phosphate receptor ($S1P_{1,4,5}$) modulator that is in development for the treatment of immune-mediated diseases, including moderately to severely active ulcerative colitis. In the phase 2 OASIS randomised trial (NCT02447302) and open-label extension study (NCT02536404), patients with moderately to severely active ulcerative colitis who received etrasimod showed greater improvements in their modified Mayo score, clinical remission, endoscopic improvement, and symptom relief, beginning as early as week 2, compared with patients who received placebo. We searched PubMed on Oct 10, 2022, using search strings with the terms "etrasimod," "ulcerative colitis," "S1P receptor," and "treat-through design," with no language or date restrictions to contextualise our findings. This search revealed that, to date, there are no published, phase 3 placebo-controlled trials that use a treat-through design of an S1P receptor modulator in patients with ulcerative colitis.

Added value of this study

ELEVATE UC 52 and ELEVATE UC 12 are two phase 3 randomised trials of etrasimod in patients with moderately to severely active ulcerative colitis. To our knowledge, ELEVATE UC 52 is the first phase 3 treat-through design trial of S1P receptor modulators in which all patients enrolled in the trial were included in the efficacy evaluation at the end of the 40-week maintenance period without re-randomisation of responders at the end of the 12-week induction period. Etrasimod treatment resulted in improvements in the primary endpoint of clinical remission in both the ELEVATE UC 52 and ELEVATE UC 12 trials and was well tolerated by patients. Key secondary endpoints for both trials, including endoscopic improvement, symptomatic remission, and endoscopic improvement–histological remission, and sustained clinical remission and corticosteroid-free clinical remission in ELEVATE UC 52, were achieved in patients treated with etrasimod.

Implications of all the available evidence

The results of these trials show the potential of etrasimod as an oral, once-daily treatment option for patients with moderately to severely active ulcerative colitis. Although the past decade has not seen the treat-through design readily used in phase 3 ulcerative colitis programmes, the outcomes of ELEVATE UC 52 suggest that this is an appropriate study design for assessment of the safety and efficacy of new potential treatments for ulcerative colitis.

T cells in the gastrointestinal tract are characteristic of ulcerative colitis. Sphingosine 1-phosphate (S1P) is a membrane-derived lysophospholipid signalling molecule that is involved in pathophysiological processes via extracellular activation of the cell surface expressed S1P receptor subtypes 1–5 ($S1P_1$–$S1P_5$).[3,5] Modulation of $S1P_1$ receptors reversibly sequesters specific lymphocyte subsets in lymph nodes, resulting in fewer peripheral immune cells available to traffic to sites of inflammation, such as the gastrointestinal tract in patients with ulcerative colitis.[6,7] The first-generation non-selective S1P receptor modulator fingolimod was approved for the treatment of patients with multiple sclerosis in 2010.[8] The interaction of fingolimod with $S1P_2$ and $S1P_3$ has been associated with serious adverse events, including reduced pulmonary function, malignancies, macular oedema, and cardiovascular effects.[6,8,9] Ozanimod, a selective $S1P_{1,5}$ receptor modulator, is approved for the treatment of multiple sclerosis and ulcerative colitis. Ozanimod avoids interaction with $S1P_2$ and $S1P_3$, potentially reducing the risk of serious adverse events versus fingolimod.[10] The functions of $S1P_4$ and $S1P_5$ are not well understood, but evidence suggests they are involved in dendritic cell trafficking and natural killer cell localisation, respectively.[11,12] Because of an on-target, $S1P_1$-associated first-dose heart-rate-lowering effect, ozanimod requires a 7-day up-titration regimen in which the identified effective dose is first used on day 8,[10] potentially delaying the onset of symptom relief in patients with ulcerative colitis. The ozanimod parent compound forms major active metabolites that are inhibitors of monoamine oxidase B, which might increase the risk of drug–drug and food interactions.[13] These factors leave a continuing unmet need for the development of a new generation of selective S1P receptor modulators.

Etrasimod, a once-daily, oral, S1P receptor modulator that selectively activates $S1P_{1,4,5}$, with no detectable activity on $S1P_{2,3}$, is in development for the treatment of immune-mediated diseases, including ulcerative colitis. Etrasimod is dosed without an up-titration regimen and phase 1 studies suggest that etrasimod is metabolised by three different cytochrome P450s with approximately equal contributions, potentially limiting the risk of drug–drug and food interactions.[14] Treatment with etrasimod (2 mg, once daily) showed significant benefit versus placebo in the 12-week, phase 2 OASIS study[15] and the 36-week, open-label extension study.[16] Here, we report the results of ELEVATE UC 52, which comprised a 12-week induction period followed by a 40-week maintenance period with a treat-through design, and ELEVATE UC 12, which comprised a 12-week induction period only. In these two phase 3 trials, we aimed to evaluate the safety and efficacy of etrasimod in adult patients with moderately to severely active ulcerative colitis.

Methods

Study design and patients

We did two randomised, multicentre, double-blind, placebo-controlled, phase 3 trials. Patients in ELEVATE UC 52 were enrolled from 315 centres in 40 countries. Patients in ELEVATE UC 12 were enrolled from 407 centres in 37 countries. The protocols were approved by the institutional review board at each participating

centre. All patients provided written informed consent. Both trials were done in accordance with the principles of the Declaration of Helsinki.

In both trials, eligible patients (aged 16–80 years) had moderately to severely active ulcerative colitis (confirmed by endoscopy with ≥10 cm rectal involvement and on the basis of a modified Mayo score [MMS] of 4–9 with a centrally read endoscopic subscore ≥2 and rectal bleeding subscore ≥1) and a documented history of inadequate response, loss of response, or intolerance of at least one therapy approved for the treatment of ulcerative colitis. Patients with isolated proctitis (<10 cm rectal involvement) at baseline who met other eligibility criteria (based on an MMS of 4–9 with a centrally read endoscopic subscore ≥2 and rectal bleeding subscore ≥1) could enrol in both trials, with enrolment capped at 15% of total patients. Patients were permitted to receive concomitant treatment for ulcerative colitis with stable doses of oral aminosalicylates or corticosteroids (prednisone [≤20 mg/day], budesonide [≤9 mg/day], or equivalent), provided that they were on a stable dose 2 weeks or 4 weeks before trial screening, respectively. Investigators were directed to taper corticosteroids in ELEVATE UC 52 after the week 12 assessment. Exclusion criteria included previous treatment with at least three biological agents or at least two biologicals plus a Janus kinase (JAK) inhibitor approved for the treatment of ulcerative colitis; a high risk of requiring a colectomy in the next 3 months (per investigator); a clinically relevant cardiac condition (a history of myocardial infarction, stroke, or second-degree or third-degree atrioventricular block); a history of opportunistic infections or macular oedema; or pregnancy or lactation. Detailed inclusion and exclusion criteria are provided in the appendix (pp 20–26).

Demographics including sex at birth were collected at screening as reported by the patient. Only male or female options for sex were provided.

Randomisation and masking

In both trials, patients were randomly assigned (2:1) to etrasimod or placebo, stratified by previous exposure to biologicals or JAK inhibitor therapy (yes *vs* no), baseline corticosteroid use (yes *vs* no), and baseline disease activity (MMS; 4–6 *vs* 7–9). Participants were centrally assigned to randomised study treatment using an interactive web response system (IWRS) using block randomisation methods stratified by naive to biologic or JAK inhibitor therapy at study entry (yes *vs* no), baseline corticosteroid use (yes *vs* no), and baseline disease activity (MMS 4 to 6 *vs* 7 to 9). Block randomisation schedules were computer generated by a vendor with a block size of 6 in a randomisation ratio of 2:1 and distributed to the IWRS vendor (endpointClinical) for participant randomisation. This was a double-blind study with limited access to the randomisation code. The study treatment and placebo tablets and bottles were identical in physical appearance. The treatment each patient received was not disclosed to the investigator, study site staff, patient, sponsor personnel involved with the conduct of the study (with the exception of the clinical supply staff and designated safety staff), or study vendors. LabCorp Drug Development (a subcontractor to the IWRS vendor) generated the live randomisation schedules. Site personnel enrolled participants in the IWRS. The IWRS assigned participants to the trial groups per live randomisation schedules. LabCorp Drug Development didn't have any involvement in the rest of the trial. The IWRS vendor was involved in the rest of the trial for drug supply services (eg, supply and resupply and shipment). Site personnel were involved in participant care and performing trial procedures throughout the trial; however, they were masked to treatment assignment.

The IWRS housed treatment codes and bottle numbers for study treatment. In case of an emergency, the investigator had the sole responsibility for determining if unmasking of a participant's treatment assignment was warranted to provide appropriate medical care. Participant safety was always the first consideration in making such a determination. The IWRS was programmed with blind-breaking instructions to guide the investigator on how to obtain treatment assignment in the event of an emergency unmasking. The investigator was requested to contact the medical monitor promptly in case of any treatment unmasking. If a participant's treatment assignment was unmasked, the sponsor was to be notified within 24 h after unmasking. The date and reason for the unmasking were recorded in the source documentation and electronic case report form, as applicable. Investigators broke the masking for four participants: one in ELEVATE UC 12 (on etrasimod) and three in ELEVATE UC 52 (on etrasimod).

See Online for appendix

Procedures

Patients received once-daily oral treatment with etrasimod 2 mg or placebo. ELEVATE UC 52 had a treat-through design that comprised a 12-week induction period followed by a 40-week maintenance period and 4-week follow-up period. Beginning at week 12, all patients could continue their randomly assigned treatment into a 40-week maintenance period; those whose disease had not improved or had worsened compared with baseline (on the basis of investigator judgement), could discontinue treatment and, if objective disease worsening criteria were met (having either or both rectal bleeding subscore ≥2 or rectal bleeding plus stool frequency subscores ≥4 at two timepoints ≥7 and ≤14 days apart), enrol in an open-label extension study (NCT03950232). At the end of week 52, patients could enrol in the open-label extension study (figure 1).

ELEVATE UC 12 comprised a 12-week induction period and a 4-week follow-up period. At the end of week 12, patients could enrol in the open-label extension study (NCT03950232). In either trial, patients who did not enrol in the open-label extension study entered a 4-week follow-up period with visits at week 2 and week 4.

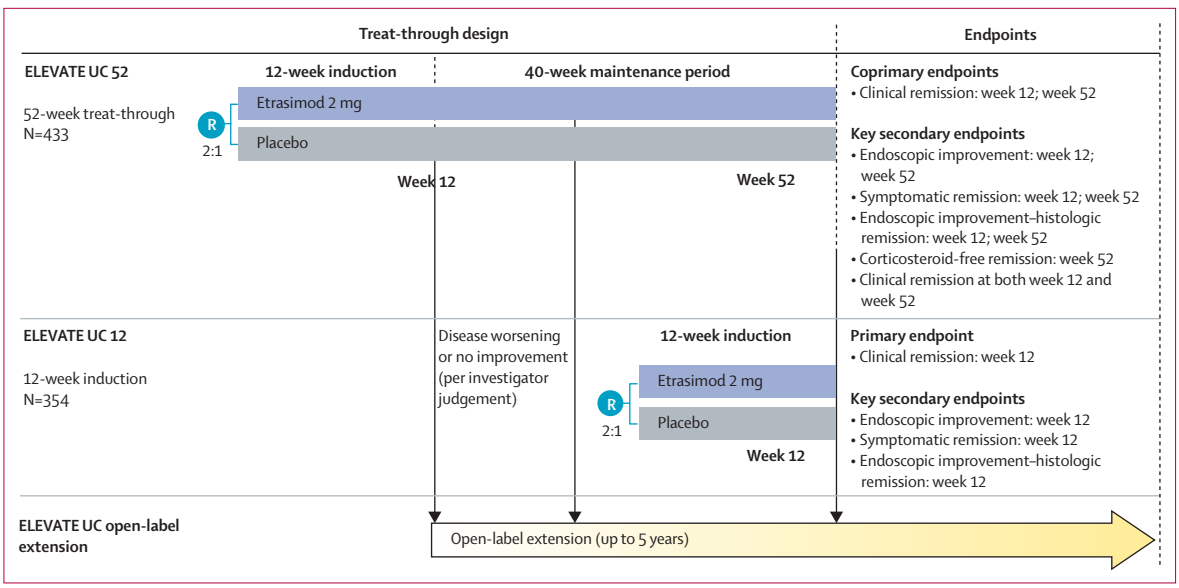

Figure 1: **ELEVATE UC 52 and ELEVATE UC 12 trial schematic**
R=randomisation.

Patient demographics and clinical characteristics were collected by study staff during the screening period. MMS, physician's global assessment, and quality-of-life assessments were collected at weeks 0, 12, and 52 for patients in ELEVATE UC 52 and weeks 0 and 12 for patients in ELEVATE UC 12. The complete schedule of assessments and procedures are listed in the appendix (p 27).

MMS was a composite of three assessments (stool frequency, rectal bleeding, and endoscopic subscore), each rated from 0 (none) to 3 (most severe);[17] overall MMS scores range from 0–9, with higher scores indicating greater activity. The total Mayo score was defined as the sum of the rectal bleeding subscore, stool frequency subscore, endoscopic subscore, and physician's global assessment subscore (each subscore on a scale of 0–3); total scores range from 0–12, with higher scores indicating greater activity. Clinical remission was defined as a composite of stool frequency subscore=0 (or stool frequency subscore=1 with a ≥1-point decrease from baseline), rectal bleeding subscore=0, and endoscopic subscore of 1 or less by independent, centrally read assessment (without friability).

Because of the COVID-19 pandemic, modifications were implemented in accordance with regulatory guidance to allow study continuity, maintain compliance with Good Clinical Practice, and ensure data integrity while protecting the safety of patients and clinical site staff.

Outcomes

The coprimary endpoints in ELEVATE UC 52 were the proportion of patients who achieved clinical remission at week 12 (induction period) and week 52 (maintenance period). The primary endpoint for ELEVATE UC 12 was the proportion of patients in clinical remission at the end of the 12-week induction period. Endoscopy images and video recordings of the entire endoscopic procedure were obtained for each endoscopy and were sent for central reading for assessment. The endoscopic subscore was evaluated by the investigator and the central reader. The central read was used for determination of efficacy endpoints.

Key secondary endpoints for ELEVATE UC 52 included endoscopic improvement (endoscopic subscore ≤1, without friability), symptomatic remission (stool frequency subscore=0 [or stool frequency=1 with a ≥1-point decrease from baseline] and rectal bleeding subscore=0), and endoscopic improvement–histological remission (endoscopic subscore ≤1, without friability) with histological remission (Geboes Index score <2·0[18]) at week 12 and at week 52 (referred to as mucosal healing in the protocol and statistical analysis plan). Corticosteroid-free (clinical remission at week 52 and corticosteroid free for ≥12 weeks before week 52) and sustained clinical remission (clinical remission at both weeks 12 and 52) were additional key secondary endpoints assessed at week 52. Other prespecified endpoints included clinical response (≥2-point and ≥30% decrease from baseline in MMS and a ≥1-point decrease from baseline in rectal bleeding subscore or an absolute rectal bleeding subscore ≤1) at weeks 12 and 52; 4-week and 12-week corticosteroid-free remission among patients with baseline corticosteroid use (clinical remission at week 52 and corticosteroid free for at least 4 weeks or 12 weeks immediately before week 52); endoscopic normalisation at week 12 and week 52 (endoscopic subscore=0); and change from baseline per visit in symptomatic remission, rectal bleeding subscores, stool frequency subscores, rectal bleeding plus stool frequency composite subscores,

lymphocyte counts, faecal calprotectin, and high-sensitivity C-reactive protein.

Key secondary endpoints for ELEVATE UC 12 included endoscopic improvement, symptomatic remission, and endoscopic improvement–histological remission at week 12. Other prespecified endpoints included clinical response at week 12, endoscopic normalisation at week 12, and change from baseline per visit in symptomatic remission, rectal bleeding subscores, stool frequency subscores, rectal bleeding plus stool frequency composite subscores, lymphocyte counts, faecal calprotectin, and high-sensitivity C-reactive protein.

The full list of protocol-defined primary and secondary endpoints is included in the appendix (pp 16–19; with endpoints examined in this study defined on appendix pp 30–32). To ensure that key data from both trials were presented, we prioritised reporting of primary and key secondary efficacy endpoints, and additional secondary efficacy endpoints that were most relevant for clinical decision making. Subsequent publications will report data not included in this manuscript.

Safety was evaluated by adverse event monitoring, clinical laboratory findings, physical examinations, pulmonary function tests, and ophthalmological examinations. Safety endpoints evaluated in both trials included the incidence and severity of adverse events, the incidence and severity of laboratory abnormalities and change from baseline in laboratory values (haematology, serum chemistry, coagulation, and urinalysis), and the incidence of clinically significant vital sign abnormalities and changes from

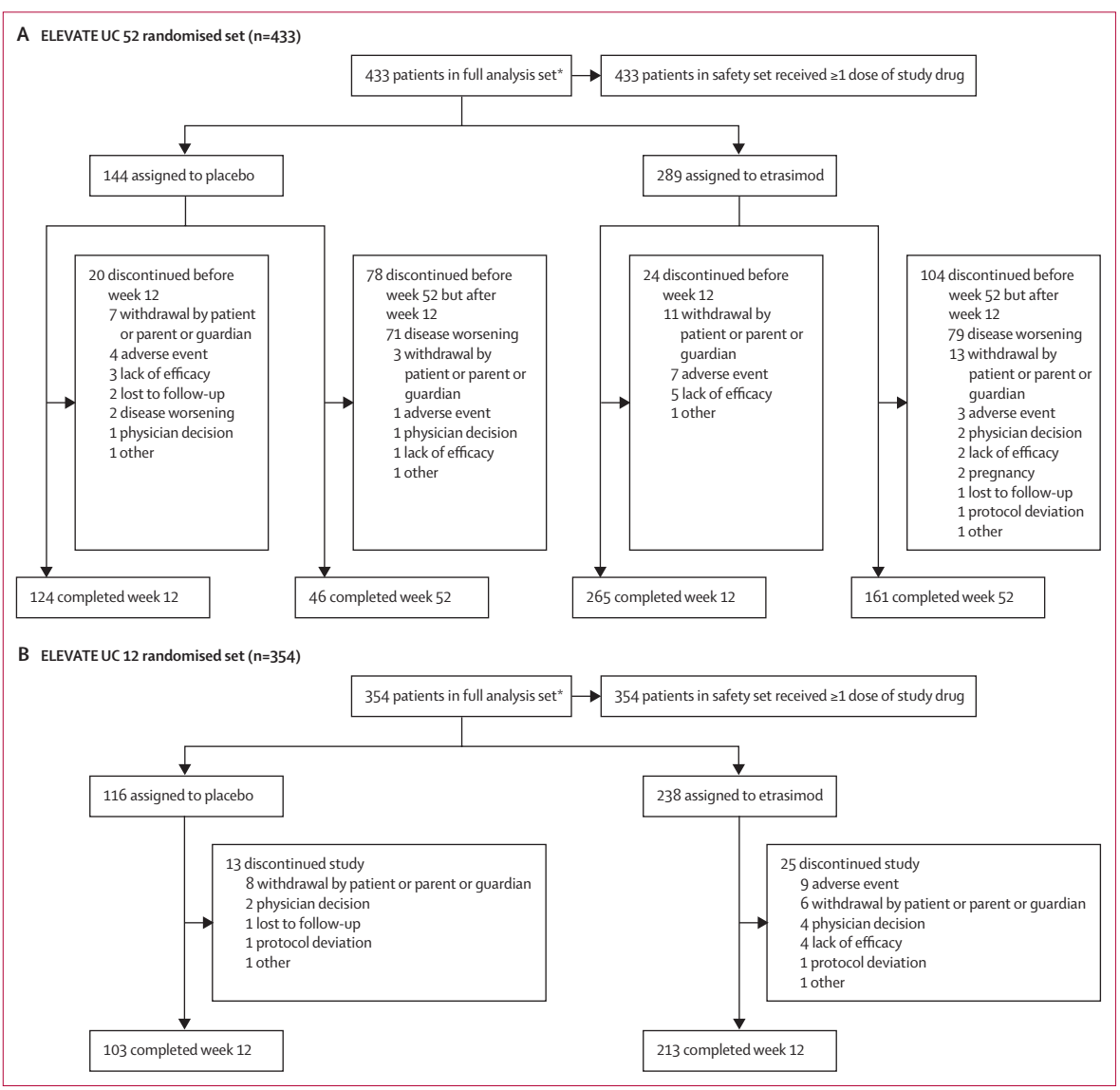

Figure 2: **Trial profiles for patients in ELEVATE UC 52 (A) and ELEVATE UC 12 (B)**
*The full analysis set comprised all randomly assigned patients (modified Mayo score 4–9) who received at least one dose of study treatment.

	ELEVATE UC 52		ELEVATE UC 12	
	Etrasimod group (n=289)	Placebo group (n=144)	Etrasimod group (n=238)	Placebo group (n=116)
Age, years	41·2 (14·0)	38·9 (14·0)	40·3 (13·5)	40·4 (13·3)
Sex				
Female	137 (47%)	56 (39%)	103 (43%)	43 (37%)
Male	152 (53%)	88 (61%)	135 (57%)	73 (63%)
Race				
White	256 (89%)	129 (90%)	176 (74%)	88 (76%)
Asian	22 (8%)	9 (6%)	47 (20%)	25 (22%)
Black or African American	6 (2%)	3 (2%)	2 (1%)	2 (2%)
Other combined*	5 (2%)	3 (2%)	13 (5%)	1 (1%)
Ethnicity				
Non-Hispanic	275 (95%)	136 (94%)	226 (95%)	107 (92%)
Hispanic	12 (4%)	7 (5%)	10 (4%)	9 (8%)
Not reported	1 (<1%)	1 (1%)	1 (<1%)	0
Unknown	1 (<1%)	0	1 (<1%)	0
BMI, kg/m²	25·4 (5·5)	25·3 (5·4)	24·3 (4·8)	25·2 (4·4)
Duration of ulcerative colitis, years	7·5 (8·0)	5·9 (5·5)	7·3 (6·6)	7·7 (7·3)
Extent of ulcerative colitis (per investigator)				
Isolated proctitis	22 (8%)	6 (4%)	15 (6%)	12 (10%)
Left-sided colitis or proctosigmoiditis	172 (60%)	90 (63%)	146 (61%)	63 (54%)
Pancolitis	93 (32%)	47 (33%)	77 (32%)	41 (35%)
Missing	2 (1%)	1 (1%)	0	0
MMS				
4–6	113 (39%)	57 (40%)	109 (46%)	53 (46%)
7–9	176 (61%)	87 (60%)	129 (54%)	63 (54%)
4	15 (5%)	9 (6%)	16 (7%)	4 (3%)
5–9	274 (95%)	135 (94%)	222 (93%)	112 (97%)
MMS	6·7 (1·2)	6·7 (1·2)	6·6 (1·2)	6·6 (1·2)
Total Mayo score	9·0 (1·5)	9·0 (1·4)	8·7 (1·5)	8·8 (1·5)
Endoscopic subscore=3	163 (56%)	88 (61%)	129 (54%)	60 (52%)
High-sensitivity C-reactive protein, mg/L	9·6 (15·5)	10·8 (18·1)	7·5 (12·6)	8·1 (15·7)
Faecal calprotectin, mg/kg	2459·8 (4520·9)	2640·3 (5325·0)	2333·5 (5010·0)	2053·5 (4251·5)
Previous ulcerative colitis treatment				
Corticosteroids	224 (78%)	101 (70%)	177 (74%)	98 (84%)
5-aminosalicylic acid	197 (68%)	95 (66%)	149 (63%)	85 (73%)
Thiopurines	108 (37%)	49 (34%)	89 (37%)	49 (42%)
Exposed to biologicals or JAK inhibitor†	108 (37%)	55 (38%)	89 (37%)	43 (37%)
TNFα antagonists	60 (21%)	31 (22%)	57 (24%)	29 (25%)
Anti-integrin antibodies	28 (10%)	19 (13%)	33 (14%)	10 (9%)
Anti-IL-12 or anti-IL-23 antibodies	6 (2%)	1 (1%)	5 (2%)	4 (3%)
JAK inhibitors	20 (7%)	9 (6%)	15 (6%)	9 (8%)
Concomitant ulcerative colitis treatment at baseline				
Corticosteroids	96 (33%)	46 (32%)	78 (33%)	38 (33%)
5-aminosalicylic acid	228 (79%)	111 (77%)	201 (84%)	94 (81%)

Data are mean (SD) or n (%). JAK=Janus kinase. MMS=modified Mayo score. *Comprises American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other. †As reported by investigators during the screening period.

Table 1: **Baseline demographic and clinical characteristics (full analysis set)**

baseline. The severity of each adverse event was assessed at the onset by a nurse or physician. When recording the outcome of the adverse event, the maximum severity of the adverse event was also recorded according to the Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

Sample sizes for ELEVATE UC 52 and ELEVATE UC 12 were determined using a two-group Fisher's exact test, a two-sided significance level of 0·05, and a 2:1 randomisation ratio. To achieve at least 90% power to detect a 12·5% difference in clinical remission between the etrasimod group and placebo group at week 12 in either trial and a 13·5% difference at week 52 in ELEVATE UC 52, 420 patients (280 assigned to etrasimod and 140 assigned to placebo) were required for the coprimary endpoints in ELEVATE UC 52 and 330 patients (220 assigned to etrasimod and 110 assigned to placebo) for the primary endpoint in ELEVATE UC 12. Additional details regarding statistical analysis are provided in the appendix (pp 27–29).

Consistent with the statistical analysis plan, the primary efficacy analysis was done in patients with a baseline MMS of 5–9 (to align with regulatory body feedback), comprising randomly assigned patients who received at least one dose of study treatment. Efficacy analyses were done using the Cochran-Mantel-Haenszel method, stratified by previous exposure to biological or JAK inhibitor therapy (yes *vs* no), baseline corticosteroid use (yes *vs* no), and baseline disease activity (MMS; 4–6 *vs* 7–9). Primary and key secondary endpoints were controlled for multiplicity via parallel gatekeeping procedures that preserved the familywise type I error rate at 5%;[19,20] significant values for other prespecified endpoints were nominal. Results were expressed as the number of patients in each binary endpoint, percentages, and differences in percentages between the etrasimod and placebo groups with associated 95% CIs and p values. All p values were unadjusted. Two-sided p≤0·05 was considered to indicate a significant difference.

Patients who discontinued the trials for reasons other than worsening disease, lack of efficacy, or ulcerative colitis-related adverse events were considered to have missing data; otherwise, they were considered to have a known outcome of non-response. In the analysis of the primary endpoint and all binary responder-type endpoints, patients with missing data were considered non-responders. For continuous or score-based endpoints, data were analysed as observed in a mixed-effect model with repeated measures. Safety data were listed and summarised by treatment group in all patients who received at least one dose of study treatment.

An external independent data monitoring committee was used to monitor the safety of participants and to enhance the integrity and credibility of the study.

All analyses were done using SAS (version 9.4 or later). ELEVATE UC 52 and ELEVATE UC 12 are registered

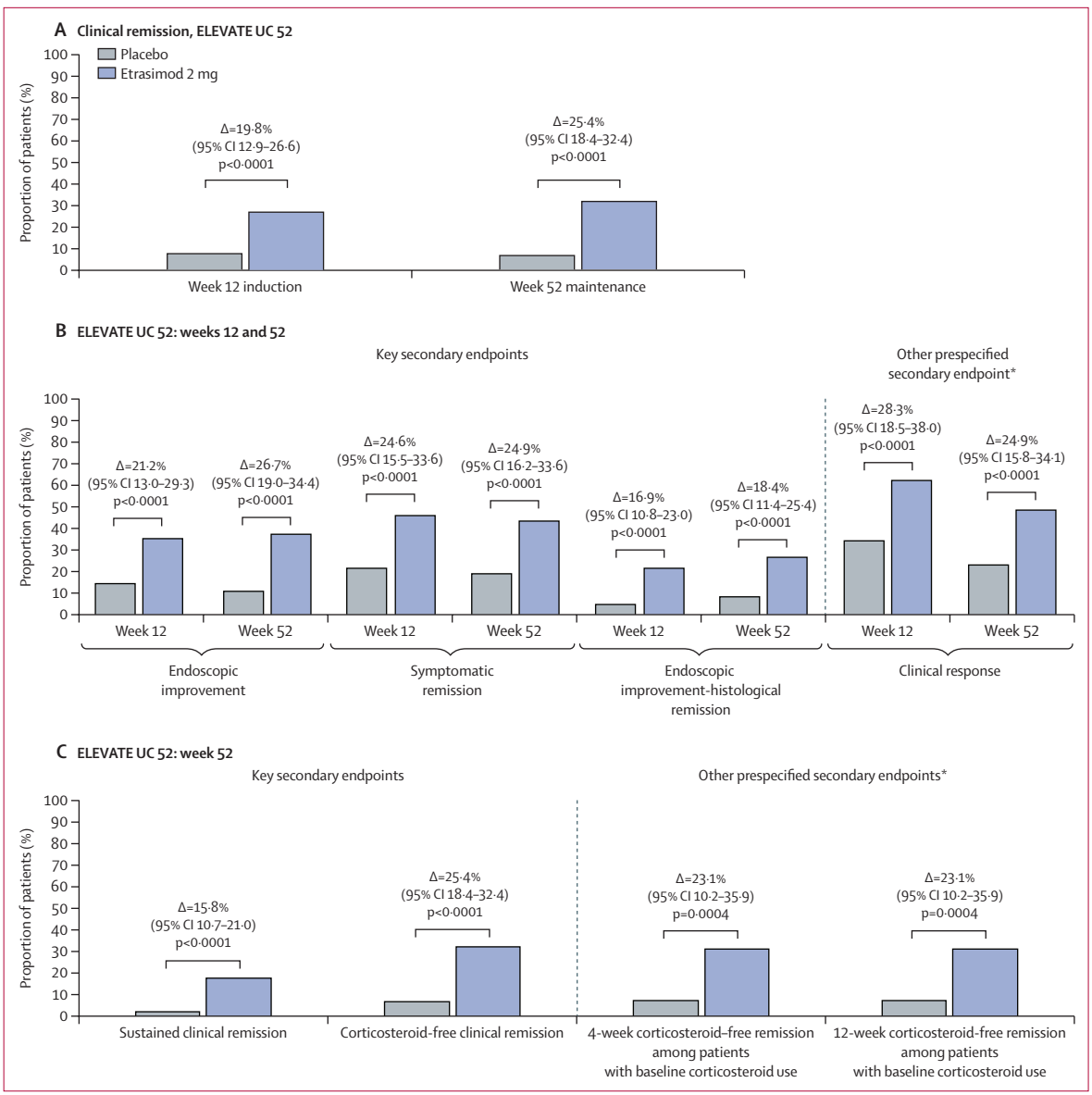

Figure 3: **Coprimary endpoints of clinical remission at week 12 and at week 52 (A), key secondary and additional prespecified secondary endpoints at week 12 and week 52 (B), and key secondary and additional prespecified endpoints of sustained remission and corticosteroid-free remission at week 52 in ELEVATE UC 52 (C)**

Patients with ulcerative colitis included those with a modified Mayo score of 5–9. *Significance is represented using unadjusted p values.

with ClinicalTrials.gov, NCT03945188 and NCT03996369, respectively.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and review and approval of the manuscript.

Results

Patients in ELEVATE UC 52 were enrolled between June 13, 2019, and Jan 28, 2021. Patients in ELEVATE UC 12 were enrolled between Sept 15, 2020, and Aug 12, 2021. ELEVATE UC 52 and ELEVATE UC 12 screened 821 patients and 606 patients, respectively, with 433 and 354 subsequently undergoing random assignment (figure 2).

The full analysis set of ELEVATE UC 52 comprised 289 patients assigned to etrasimod and 144 to placebo. A total of 265 (92%) patients in the etrasimod group and 124 (86%) patients in the placebo group completed the induction period and 161 (56%) patients and 46 (32%) patients, respectively, completed week 52. The most common reason for discontinuation in either study group during the induction period was withdrawal by the

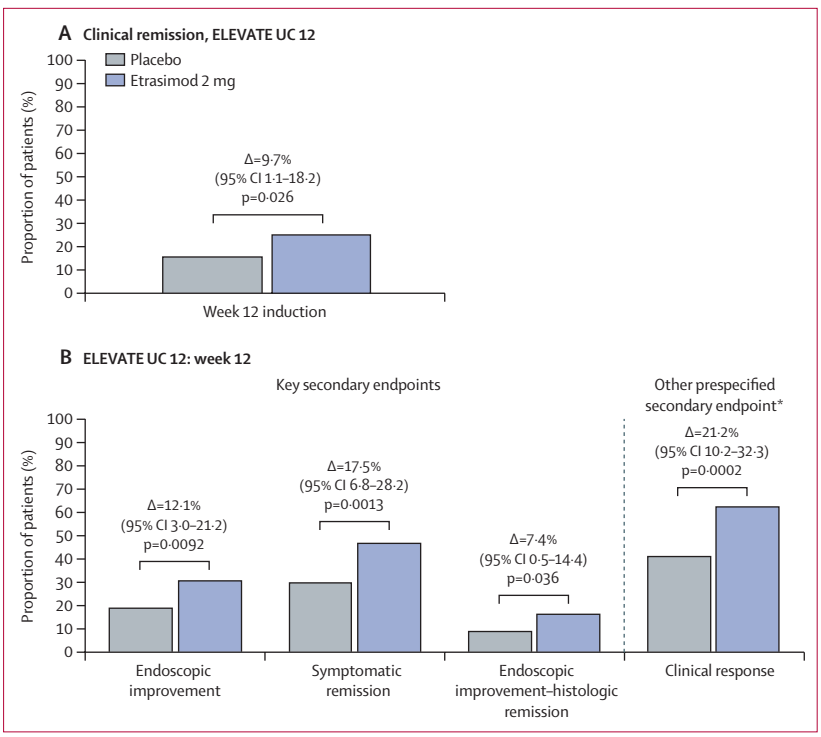

Figure 4: **The primary endpoint of clinical remission at week 12 (A) and key secondary and additional prespecified secondary endpoints at week 12 (B) in ELEVATE UC 12**
Patients with ulcerative colitis included those with a modified Mayo score of 5–9. *Significance is represented using unadjusted p values.

patient. The most common reason for discontinuation in either study group during the maintenance period was disease worsening (figure 2).

In ELEVATE UC 12, 238 patients were assigned to etrasimod and 116 to placebo, of whom 213 (89%) and 103 (89%), respectively, completed the trial. The most common reason for discontinuation in the induction period for patients in the placebo group was withdrawal by the patient and in the etrasimod group was adverse events. Baseline demographic and clinical characteristics were similar between the treatment groups in both trials (table 1). As reported by investigators during the screening period, 163 (38%) of 433 patients in ELEVATE UC 52 and 132 (37%) of 354 patients in ELEVATE UC 12 had previous biological or JAK inhibitor experience; however, based on subsequent evaluation of patient medication history, 129 (30%) of 433 patients in ELEVATE UC 52 and 118 (33%) of 354 patients in ELEVATE UC 12 had actual biological or JAK inhibitor experience.

In ELEVATE UC 52, a significantly greater proportion of patients in the etrasimod group achieved clinical remission compared with patients in the placebo group at completion of the 12-week induction period (74 [27%] of 274 patients *vs* ten [7%] of 135 patients) and at week 52 (88 [32%] of 274 patients *vs* nine [7%] of 135 patients; figure 3A).

In ELEVATE UC 52, at week 12, significant improvements with etrasimod were observed versus placebo in the three key secondary endpoints of endoscopic improvement (96 [35%] of 274 patients *vs* 19 [14%] of 135 patients), symptomatic remission (126 [46%] of 274 patients *vs* 29 [21%] of 135 patients), and endoscopic improvement–histological remission (58 [21%] of 274 patients *vs* six [4%] of 135 patients; figure 3B). Additionally, in ELEVATE UC 52 at week 12, significant improvements with etrasimod compared with placebo were observed for the other prespecified secondary endpoint of clinical response (171 [62%] of 274 patients *vs* 46 [34%] of 135 patients; figure 3B).

At week 52, all key secondary efficacy endpoints were met, including sustained clinical remission (49 [18%] of 274 patients *vs* three [2%] of 135 patients) and corticosteroid-free remission with no use of corticosteroids for at least 12 weeks among all patients regardless of corticosteroid use at baseline (88 [32%] of 274 patients *vs* nine [7%] of 135 patients; figure 3C). Similar results for corticosteroid-free remission with no use of corticosteroids for at least 12 weeks were observed for patients with documented corticosteroid use at baseline (27 [31%] of 87 patients *vs* three [8%] of 40 patients). All patients with remission at week 52 were also corticosteroid free for at least 12 weeks.

Outcomes at week 12 and week 52 in ELEVATE UC 52 for the full analysis set of patients in the overall trial population and for the cohort that excluded patients with isolated proctitis, and subgroup analyses stratified by previous biological or JAK inhibitor exposure, are presented in the appendix (pp 33–39).

In ELEVATE UC 12, 55 (25%) of 222 patients in the etrasimod group had clinical remission compared with 17 (15%) of 112 patients in the placebo group at the end of the 12-week induction period (figure 4A). In ELEVATE UC 12, at week 12, significant improvements with etrasimod compared with placebo were observed for the key secondary endpoints of endoscopic improvement (68 [31%] of 222 patients *vs* 21 [19%] of 112 patients), symptomatic remission (104 [47%] of 222 patients *vs* 33 [29%] of 112 patients), and endoscopic improvement–histological remission (36 [16%] of 222 patients *vs* ten [9%] of 112 patients; figure 4B). Additionally, at week 12, significant improvements with etrasimod compared with placebo were observed for the other prespecified secondary endpoint of clinical response (138 [62%] of 222 patients *vs* 46 [41%] of 112 patients; figure 4B).

Outcomes at week 12 in ELEVATE UC 12 for the full analysis set of patients in the overall trial population and for the cohort that excluded patients with isolated proctitis, and subgroup analyses stratified by previous biological or JAK inhibitor exposure are presented in the appendix (pp 40–43).

A greater proportion of patients treated with etrasimod had symptomatic remission compared with those treated with placebo by week 2 in ELEVATE UC 52 and week 4 in ELEVATE UC 12 (figure 5). Patients in the etrasimod group showed decreases in rectal bleeding and stool frequency subscores as early as week 2 in both trials

(appendix pp 56–59). A greater proportion of patients treated with etrasimod had endoscopic normalisation compared with patients treated with placebo at week 12 in both trials and week 52 in ELEVATE UC 52 (appendix p 44). Decreases in faecal calprotectin (appendix pp 60–61) and high-sensitivity C-reactive protein levels (appendix pp 62–63) were also observed in those treated with etrasimod versus those treated with placebo in both trials.

Consistent with the proposed mechanism of action, mean lymphocyte counts in patients treated with etrasimod decreased to around 50% of those at baseline by week 2 and were maintained throughout the treatment periods of ELEVATE UC 52 and ELEVATE UC 12 (appendix p 45). Among the small proportion of patients in the etrasimod group who completed either study and did not continue treatment in the open-label extension study (n=31), absolute lymphocyte counts returned to the normal range within 2 weeks in 15 (83%) of 18 patients after 52 weeks of treatment in ELEVATE UC 52 and ten (77%) of 13 patients after 12 weeks of treatment in ELEVATE UC 12.

Adverse events were reported in 206 (71%) of 289 patients in the etrasimod group and 81 (56%) of 144 patients in the placebo group in ELEVATE UC 52 and in 112 (47%) of 238 patients in the etrasimod group and 54 (47%) of 116 patients in the placebo group in ELEVATE UC 12 (table 2). Exposure-adjusted safety values were consistent between treatment groups in both studies (appendix pp 46–47). Most events were considered mild or moderate. In the etrasimod groups, 12 (4%) of 289 patients in ELEVATE UC 52 and 13 (5%) of 238 patients in ELEVATE UC 12 permanently discontinued study treatment because of treatment-emergent adverse events, compared with seven (5%) of 144 patients and one (1%) of 116 patients in the placebo groups of ELEVATE UC 52 and ELEVATE UC 12, respectively (table 2). The proportion of patients who had serious adverse events was low and similar across etrasimod and placebo groups in both studies (20 [7%] of 289 patients in the etrasimod group *vs* nine [6%] of 144 patients in the placebo group in ELEVATE UC 52; six [3%] of 238 patients in the etrasimod group *vs* two [2%] of 116 patients in the placebo group in ELEVATE UC 12). The most frequently reported adverse events (in ≥1% of patients) included anaemia, headache, and worsening of ulcerative colitis or ulcerative colitis flare. In both studies, overall infections, serious infections, and opportunistic infections (ie, tuberculosis and cytomegalovirus infection) were similar between the treatment groups. Across both trials, four patients had herpes zoster events (two patients treated with etrasimod in ELEVATE UC 52; and two patients treated with placebo in ELEVATE UC 12; table 2). These events were considered either mild or moderate, were localised, and did not lead to discontinuation from the study.

Adverse events of special interest were similar between the two trials (table 2). No malignancies were reported in either trial. Elevated liver enzymes were reported in both trials, with a higher incidence in the etrasimod treatment groups. No patients met Hy's Law criteria for elevated liver enzymes or bilirubin in either study. Two patients discontinued treatment in ELEVATE UC 52 because of increased alanine aminotransferase, one of whom had a history of primary sclerosing cholangitis, and the other had all transaminase tests less than 3 times the upper limit of normal (appendix pp 48–49). Bradycardia or sinus bradycardia was identified as a sponsor-designated adverse event of special interest if the heart rate was less than 40 beats per min, there were associated symptoms (eg, lightheadedness), or the event led to study discontinuation. Across both trials, nine events of bradycardia or sinus bradycardia were reported in patients receiving etrasimod—four in ELEVATE UC 52 and five in ELEVATE UC 12; no events were reported in patients receiving placebo. Of these nine events, five met the criteria for sponsor-designated adverse events of interest. Eight of the nine events were first reported on day 1 and the remaining event was reported on day 2. Two of the events of bradycardia were symptomatic (accompanied by mild or moderate dizziness) and led to

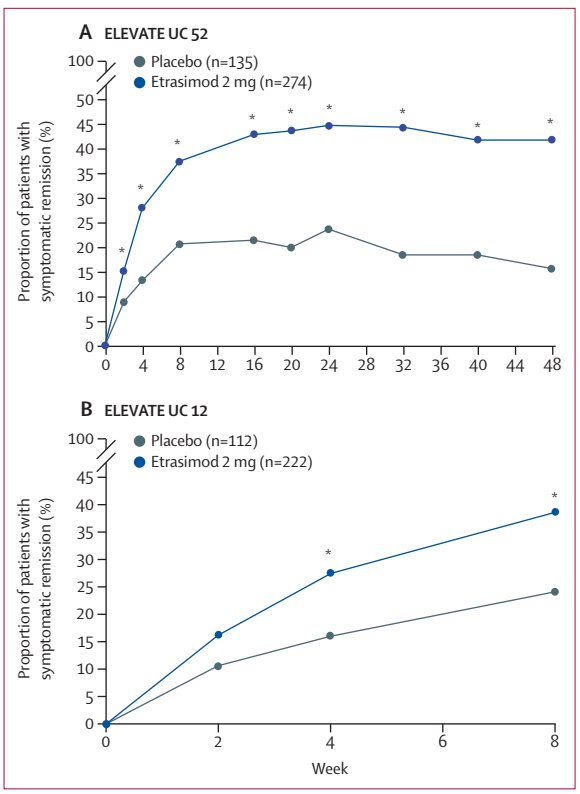

Figure 5: **Symptomatic remission over time in ELEVATE UC 52 (A) and ELEVATE UC 12 (B) (non-responder imputation)**
Patients with ulcerative colitis included those with a modified Mayo score of 5–9. *p≤0·05; data based on Cochran-Mantel-Haenszel analysis of the full analysis set (all randomly assigned patients who received at least one dose of study drug) and non-responder imputation. Significance is represented using nominal two-sided p values to test the hypothesis of the risk difference for etrasimod minus placebo being 0, based on the estimated common risk difference using Mantel-Haenszel weights.

	ELEVATE UC 52		ELEVATE UC 12	
	Etrasimod group (n=289)	Placebo group (n=144)	Etrasimod group (n=238)	Placebo group (n=116)
Any adverse events	206 (71%)	81 (56%)	112 (47%)	54 (47%)
Any serious adverse events	20 (7%)	9 (6%)	6 (3%)	2 (2%)
Any adverse event leading to study treatment discontinuation	12 (4%)	7 (5%)	13 (5%)	1 (1%)
Adverse events leading to death	0	0	0	0
Most common adverse events				
Worsening of ulcerative colitis or ulcerative colitis flare	22 (8%)	13 (9%)	9 (4%)	1 (1%)
Anaemia	24 (8%)	14 (10%)	14 (6%)	8 (7%)
Headache	24 (8%)	7 (5%)	11 (5%)	2 (2%)
Nausea	9 (3%)	2 (1%)	10 (4%)	2 (2%)
COVID-19	20 (7%)	9 (6%)	3 (1%)	3 (3%)
Dizziness	15 (5%)	1 (1%)	3 (1%)	0
Pyrexia	14 (5%)	6 (4%)	8 (3%)	3 (3%)
Arthralgia	13 (4%)	3 (2%)	4 (2%)	3 (3%)
Abdominal pain	11 (4%)	5 (3%)	3 (1%)	3 (3%)
Adverse events of special interest				
Serious infections	3 (1%)	5 (3%)	0	0
Herpes zoster	2 (1%)	0	0	2 (2%)
Opportunistic infections	0	1 (1%)	1 (<1%)	0
Hypertension	8 (3%)	1 (1%)	3 (1%)	1 (1%)
Sinus bradycardia	0	0	4 (2%)	0
Bradycardia	4 (1%)	0	1 (<1%)	0
Atrioventricular block, first degree	1 (<1%)	0	1 (<1%)	0
Atrioventricular block, second degree (Mobitz I)	1 (<1%)	0	0	0
Macular oedema	1 (<1%)	0	1 (<1%)	1 (1%)

Data are n (%). The most frequent adverse events were defined as those that occurred in ≥3% of etrasimod-treated patients and those that occurred as a greater rate in the etrasimod group versus the placebo in either study. Data were not exposure adjusted.

Table 2: **Summary of adverse events and most frequent adverse events**

study discontinuation; both events resolved without the need for pharmacological intervention. Of the seven asymptomatic events, all were reported on day 1, and three of the patients who had these events discontinued the study. One of the three asymptomatic patients who discontinued the trial had both bradycardia and asymptomatic atrioventricular block second-degree Mobitz type I on day 1. Two additional patients had asymptomatic atrioventricular block on day 1; both events were first degree (one of the two patients was discontinued). One of the atrioventricular block first-degree events was reported as an adverse event before the first study drug dose and did not change 4 h after the dose. All three events of atrioventricular block resolved without administration of interventional treatment. No atrioventricular block second-degree Mobitz type II or higher events were reported in either trial. There were no serious events of bradycardia or atrioventricular block, and no patients had a nadir heart rate less than 40 beats per min (appendix pp 50–55). 13 patients across both trials had hypertension, but none of these events led to study interruption or discontinuation.

Across both trials, three patients had macular oedema: one patient in the etrasimod group of ELEVATE UC 52 who discontinued because of the event; one patient in the placebo group of ELEVATE UC 12 who continued without study treatment interruption; and one patient in the etrasimod group of ELEVATE UC 12 (who had a preceding moderate adverse event of uveitis) and continued without study treatment interruption. All events of macular oedema resolved.

Discussion

The results of these two phase 3 trials show that once-daily, oral etrasimod 2 mg had clinical efficacy in patients with moderately to severely active ulcerative colitis at week 12 and week 52. In ELEVATE UC 52 and ELEVATE UC 12, etrasimod treatment led to a statistically significant improvement in clinical remission at week 12 and week 52. In ELEVATE UC 52, we observed an increase in the proportion of patients who had clinical remission with etrasimod versus placebo at week 52 compared with week 12, indicating a subset of patients who achieved clinical remission after completion of the induction period. All key secondary endoscopic, symptomatic, and endohistological endpoints were met, including corticosteroid-free clinical remission at week 52. All patients with remission at week 52 in ELEVATE UC 52 were no longer taking corticosteroids as part of their treatment. Patients treated with etrasimod had a rapid onset of symptom relief, with symptomatic remission as early as week 2. Patients treated with etrasimod who were naive to previous treatment with biologicals or JAK inhibitors showed clinically meaningful improvements compared with those treated with placebo for induction and maintenance efficacy endpoints. Patients previously treated with at least one biological or JAK inhibitors showed clinically meaningful improvements compared with those treated with placebo for induction and maintenance efficacy endpoints, albeit with smaller treatment effects. These results are consistent with those observed in other advanced ulcerative colitis therapy trials that included biological-naive and biological-experienced patients. The safety profile up to 52 weeks was consistent with previous studies of etrasimod.

Etrasimod is among a new class of small-molecule S1P receptor modulators that target immune-mediated inflammatory diseases such as ulcerative colitis. Our efficacy results for both induction and maintenance are in line with all advanced therapeutic classes for the treatment of ulcerative colitis, including TNFα antagonists,[21,22] anti-integrin antibodies,[23] anti-IL-12/23 antibodies,[24] JAK inhibitors,[25,26] or $S1P_{1,5}$ receptor modulators.[10] When contextualising our maintenance efficacy results in ELEVATE UC 52, differences in clinical trial design should be noted. After the ACT 1[21] and ULTRA 2[22] anti-TNFα clinical studies, which had treat-

through designs, all placebo-controlled phase 3 clinical trials that assessed maintenance efficacy in patients with ulcerative colitis had responder re-randomisation designs. Treat-through design studies are consistent with clinical practice, where treatment is not interrupted after a fixed induction period with a potential change to placebo after response, and have been used in studies of S1P receptor modulators in other disease states.[8] This study design allows for an extended placebo-controlled observation period and evaluation of response to treatment beyond the standard induction timepoint. In contrast to responder re-randomisation studies, treat-through design studies do not allow for evaluation of the efficacy of continuing treatment to maintain an induction response versus switching to placebo. Cross-trial comparisons should be evaluated cautiously, as relative efficacy can only be definitively determined by well-designed head-to-head randomised trials.

In both ELEVATE UC 52 and ELEVATE UC 12, etrasimod showed a favourable safety profile consistent with previous studies. S1P receptor modulators have been shown to maintain components of immune function, which might provide a measure of immunosurveillance not seen with other classes of advanced treatments.[27] Previous reports in healthy volunteers suggest that etrasimod partly reduced circulating levels of specific subsets of adaptive immune cells (T cells and B cells) with no notable effects on natural killer cells and monocytes, innate immunity components that are involved in immune surveillance.[28] Indeed, in the etrasimod development programme, we did not observe an increased incidence of infections (overall infections, herpes zoster, opportunistic, or serious infections) in patients treated with etrasimod compared with patients treated with placebo. This finding contrasts with other classes of advanced ulcerative colitis treatments, which are associated with an increased risk of serious infections.[3,4,21,22,26] Transient, first-dose heart rate reduction or conduction aberrations are known effects of S1P receptor modulators.[29,30] As a result, approved labelling for other S1P receptor modulators recommends a pre-first dose electrocardiogram to identify patients with pre-existing cardiac conduction abnormalities. To minimise these first-dose heart rate effects, some previous S1P receptor modulator studies used a dose-titration phase, delaying administration of the effective dose and the largest heart rate decrease until day 8.[10] In our studies, etrasimod was initiated with the full 2-mg dose on day 1. The overall cardiovascular profile of etrasimod was similar to other S1P receptor modulators that had a dose-titration phase.[9,10] Most events of bradycardia in our trials were mild and asymptomatic. All but one event of bradycardia or atrioventricular conduction delay were reported on day 1 of dosing, and no events were reported after day 2. All events resolved without intervention. Importantly, no serious events of bradycardia or atrioventricular block were reported. S1P receptor modulators have been associated with an increased risk of macular oedema.[13] In approved labelling for other S1P receptor modulators, an ophthalmic evaluation of the fundus, including the macula, is recommended in patients with a history of diabetes, macular oedema, or uveitis.[13] The incidence of macular oedema in our trials was low and similar across treatment groups. No malignancies were reported. Data from the ongoing 5-year open-label extension will provide additional longer-term follow-up information to further elucidate the etrasimod safety profile.

Etrasimod has some distinct features that separate it from other S1P receptor modulators, notably its half-life of approximately 30 h, resulting in a relatively fast wash-out period of 1 week.[15,31] Presumably due to the fast wash-out period, in both ELEVATE studies absolute lymphocyte counts returned to the normal range for around 80% of patients within 2 weeks after cessation of treatment, which was the earliest planned follow-up visit. Ozanimod has a long-acting active metabolite with a half-life of up to 11 days, requiring up to 55 days (five half-lives) for complete wash-out after treatment cessation. The lingering effects of the active metabolite keep peripheral lymphocyte levels below the normal range in 80–90% of patients up to 90 days after treatment cessation.[32] The faster wash-out for etrasimod might be important for family planning purposes, as there is a paucity of data on the effect of S1P receptor modulators on pregnancy in humans. Additionally, the rapid lymphocyte recovery observed after cessation of etrasimod treatment might be valuable in updating vaccinations and providing a margin of safety in situations where the rate of immune reconstitution is critical.

Our study results should be interpreted in the context of some limitations. Because of the duration of the studies, any conclusions surrounding long-term safety are restricted. Notably, ELEVATE UC 12 took place entirely during the COVID-19 pandemic, whereas a large portion of patients in ELEVATE UC 52 were enrolled before the pandemic, which might have affected patient behaviour, potentially affecting the results.

In conclusion, treatment with etrasimod 2 mg was well tolerated and effective as an induction and maintenance therapy for patients with moderately to severely active ulcerative colitis. As an orally administered small molecule with once-daily dosing, durable efficacy, and a favourable safety profile, etrasimod is a treatment option with a unique combination of attributes that might address the persistent unmet needs of patients with ulcerative colitis.

Contributors

All authors meet the International Committee of Medical Journal Editors criteria for authorship for this Article, take responsibility for the integrity of the work as a whole, were involved in drafting and critical review of the manuscript, and approved the final version for submission. WJS, SV, LP-B, MCD, JP, BES, GD, SD, and BGF conceived and designed the study. AY, TR, FB, MC, DCW, and SSc did the research. WJS, SV, LP-B, MCD, JP, SSc, SSl, FC, KS, CJR, AY, MC, DCW, BES, GD, SD, MG, and BGF analysed the data. KS and CJR accessed and verified the underlying data. All authors had full access to the data, were involved in drafting the manuscript and its revisions, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and fidelity of the trials to the protocols.

Declaration of interests

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Data sharing

These studies were preregistered with an analysis plan at ClinicalTrials.gov (NCT03945188 and NCT03996369). 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 deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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