



REVIEW

Etrasimod: Review of the efficacy and therapeutic prospects of a new oral therapy for the treatment of ulcerative colitis



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Abstract Etrasimod is a synthetic, non-biological, orally administered small molecule sphingosine-1-phosphate receptor (S1PR) modulator. Etrasimod was approved by the Food and Drug Administration in 2023 and by the European Medicine Agency in 2024, constituting a new therapeutic option for the treatment of moderately to severely active ulcerative colitis in patients 16 years of age and older in the European Union. Its efficacy and tolerability have been demonstrated in several clinical trials both as induction and maintenance treatment, as well as in long-term extension studies. This article reviews the pharmacodynamic characteristics of etrasimod, its main differences with biological drugs and other small molecules (janus kinases inhibitors), as well as its clinical efficacy including certain subpopulations such as patients with isolated ulcerative proctitis, and the impact on their quality of life.

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PALABRAS CLAVE

Etrasimod;
Fármacos biológicos;
Inhibidores JAK;
Colitis ulcerosa;
Modulador del receptor de S1P;
Proctitis

Etrasimod: revisión de la eficacia y las perspectivas terapéuticas de una nueva terapia oral para el tratamiento de la colitis ulcerosa

Resumen Etrasimod es una molécula pequeña, sintética, no biológica, de administración oral, que modula el receptor de la esfingosina-1-fosfato (S1PR, del inglés). Etrasimod fue autorizado por la *Food and Drug Administration* en 2023 y por la *European Medicines Agency* en 2024, constituyendo una nueva opción terapéutica para pacientes a partir de 16 años con colitis ulcerosa activa de moderada a grave en la unión europea. Su eficacia y tolerabilidad han sido demostradas en varios ensayos clínicos, tanto como tratamiento de inducción como de mantenimiento, así como en estudios de extensión a largo plazo. En este artículo se revisan las características

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farmacodinámicas de etrasimod, sus principales diferencias con los fármacos biológicos y otras pequeñas moléculas (inhibidores de las janus quinasas), así como su eficacia clínica (incluyendo determinadas subpoblaciones como los pacientes con proctitis ulcerosa aislada) y el impacto sobre la calidad de vida de los pacientes.

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease (IBD) characterised by inflammation of the colon mucosa. The inflammation can spread in varying ways and the course of the disease runs with alternating episodes of active flare-ups and periods of remission. The pathogenesis of UC is multifactorial, involving both genetic and environmental factors.^{1,2} Its prevalence is showing an increasing trend, especially in developed countries.²⁻⁵ In Spain, there is an estimated prevalence of approximately 90 cases of UC per 100,000 population.⁶

Current clinical practice guidelines recommend the use of aminosalicylates as first-line treatment in mild to moderate UC, and the use of corticosteroids in patients who do not respond to them.^{7,8} For patients with moderate to severe UC, the therapeutic arsenal has increased with the approval of biologic drugs and small molecules. These options include inhibitors of tumour necrosis factor (TNF; infliximab, adalimumab, golimumab), an integrin inhibitor (vedolizumab), inhibitors of interleukin-23 (mirikizumab, risankizumab) or interleukin-23 and interleukin-12 (ustekinumab), janus kinase inhibitors (JAKi; tofacitinib, filgotinib, upadacitinib), and sphingosine-1-phosphate (S1P) receptor modulators (ozanimod, etrasimod).

Despite the positive impact of these therapies in the treatment of moderate to severe UC over the past 20 years,⁹⁻¹³ there are still significant challenges in the management of this disease. A significant number of patients continue to show an insufficient or inadequate response to the available drugs, underlining the need to explore new therapeutic alternatives with innovative mechanisms of action.^{14,15} Furthermore, although current treatments may help to reduce the risk of surgery, colectomy rates remain high,¹⁶⁻¹⁸ reinforcing the urgency for new effective treatments.

Etrasimod is an orally administered small molecule that acts as a selective modulator of S1P receptors (S1PR) 1, 4 and 5. Studies evaluating its efficacy have shown it to induce and maintain clinical remission in patients with moderate to severe active UC.¹⁹⁻²² It therefore represents a promising new therapeutic option for patients who do not respond adequately or lose response over time to, or do not tolerate, conventional or biologic treatments.²³

The purpose of this article is to provide a comprehensive review of the current knowledge on the mechanism of

action and efficacy of etrasimod in the treatment of UC, highlighting its role as an innovative therapeutic alternative to address the unmet needs of this disease.

General information about etrasimod

The aetiopathogenesis of IBD involves abnormal activation of both the innate immune response mediated by numerous cells, including macrophages and natural killer cells, and the adaptive immune response mediated by different cells, among them T-lymphocytes.²⁴

In the early stages of UC, activated macrophages differentiate into proinflammatory effector cells and acquire the ability to migrate to lymph nodes and present antigens to lymphocytes, critically involved in the development of IBD.²⁵ The differentiated lymphocytes migrate from the lymph nodes to the bloodstream, and from there to the intestinal mucosa, inducing the proliferation and activation of inflammatory cells.²⁶

Sphingosine-1-phosphate is a phospholipid derived from sphingosine by the action of sphingosine kinases. It plays an important regulatory role in inflammatory processes, cell growth and survival, angiogenesis, vascular tone and permeability and lymphocyte migration, among other things. Its activity is mediated by binding to cell surface transmembrane receptors expressed on various immune cells and in different locations, such as the central nervous system, cardiovascular system, musculoskeletal system, spleen, kidneys and lungs.^{27,28}

Five S1PR subunits have been identified, the tissue distribution of which is variable: S1PR1-3 are ubiquitous, while S1PR4 is predominantly located in lymphoid tissue and S1PR5 in the central nervous system and spleen²⁹ (Fig. 1A). S1P acts on the immune system by regulating the migration of lymphocytes (mainly B and T cells) from lymph nodes into the blood and lymph, and ultimately into tissues. Within the lymph nodes, naïve CD4 and CD8 T cells are activated in the presence of antigens presented by dendritic cells. These cells migrate from the lymph nodes via a gradient of S1P, the concentration of which increases until reaching the bloodstream.²⁷ The migration process is modulated by the interaction between the S1P and the S1PR, which is present on the lymphocyte cell surface. S1P has been found to be overexpressed in experimental animal models of induced colitis and in patients with active UC.³⁰

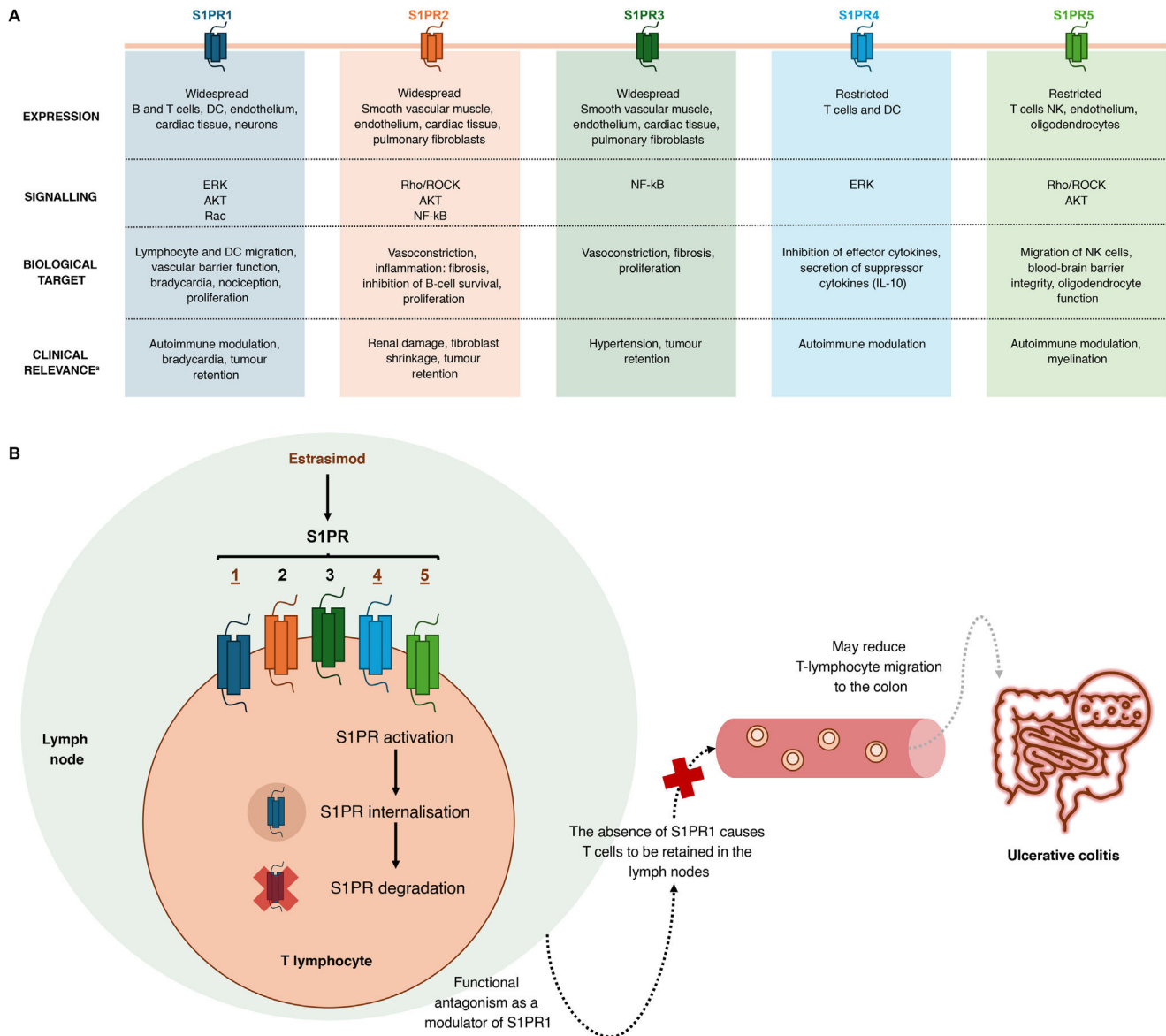


Figure 1 The role of etrasimod in ulcerative colitis. (A) Sphingosine 1-phosphate receptors: location, signalling, function and clinical relevance. (B) Functional antagonistic role of etrasimod as a modulator of sphingosine-1-phosphate receptors.^{32,59–61} ^aBased on a combination of animal and human data. DC: dendritic cells; EIHR: endoscopic improvement-histological remission; S1PR: sphingosine 1-phosphate (S1P) receptor.

Etrasimod binds to S1PR as a full agonist of S1PR1 and a partial agonist of S1PR4-5, with no detectable effect on S1PR2-3.³¹ At the same time, it acts as a functional antagonist of S1PR1 in lymphocytes by causing persistent internalisation of the receptor into the cell and its proteasome-mediated degradation. The consequent absence of S1PR1 caused by these etrasimod effects results in lymphocytes being retained in the lymph nodes, with a decrease in their concentration in peripheral blood.²⁷ Therefore, the therapeutic action of etrasimod is associated with reduced T-cell migration from lymph nodes to blood and colonic mucosa (Fig. 1B). Notably, etrasimod-induced lymphocyte depletion has differential effects on lymphocyte subpopulations, with a more pronounced decrease in cells involved in the adaptive immune response.³²

Clinical development of etrasimod in ulcerative colitis

The efficacy of etrasimod has been evaluated in one phase 2 clinical study (OASIS²¹ and two phase 3 studies (ELEVATE UC),³³ followed by their respective long-term extension studies (OASIS OLE³¹ and ELEVATE UC OLE³⁴) in patients with moderate to severe UC (Table 1).

Design of Phase 3 studies with etrasimod (ELEVATE UC)

The ELEVATE UC 52 study, comprising a 12-week induction period followed by a 40-week maintenance period in a treat-

Table 1 Clinical development of etrasimod in ulcerative colitis.

Study	Design	Inclusion criteria	Duration	Treatment	Primary endpoint	Secondary endpoints
Phase 2 clinical study (OASIS study) ²¹	Multicentre, double-blind, parallel-group, placebo-controlled study	156 patients aged 18–80 with moderate to severe UC (mMMS score 4–9, endoscopic subscore ≥ 2 and rectal bleeding subscore ≥ 1) and previously intolerant or previous failure of conventional therapies or biologics	12 weeks	52 patients received etrasimod 1 mg once daily, 50 patients etrasimod 2 mg, and 54 patients placebo	Mean MMS improvement from baseline to week 12	Proportion of patients at week 12 who achieved endoscopic improvement (defined as an endoscopic subscore of ≤ 1), improvement in the two components of the MMS (range: 0–6, including rectal bleeding and endoscopic findings), and improvement in total MMS (range: 0–12, composed of MMS plus physician's global assessment)
4 Long-term extension clinical trial (OASIS OLE study) ³¹	Patients who completed the double-blind study were eligible for inclusion in the open-label extension study		52 weeks	112 patients received etrasimod 2 mg once daily	Tolerability and long-term safety of etrasimod	Proportion of patients with clinical response, clinical remission or endoscopic improvement from week 12 to the end of therapy
Phase 3 induction study (ELEVATE UC 12) (Fig. 2) ³³	Multicentre, phase 3, randomised, double-blind, placebo-controlled clinical trial	354 patients aged 16–80 with active moderate to severe UC (confirmed by endoscopy: endoscopic subscore ≥ 2 and rectal bleeding subscore ≥ 1 and histopathology with disease extending to ≥ 10 cm from the anal verge and an mMMS score of 4–9) and an inadequate response, loss of response, or intolerance to at least one approved treatment for UC	12 weeks	238 received etrasimod 2 mg once a day and 116 placebo	Percentage of patients achieving clinical remission at week 12 (defined as a stool count subscore of 0 (or 1 with a decrease of ≥ 1 point from baseline), rectal bleeding subscore of 0 and endoscopic subscore ≤ 1 (no friability))	Percentage of patients achieving endoscopic improvement, symptom remission and endoscopic improvement/histological remission at week 12

Table 1 (Continued)

Study	Design	Inclusion criteria	Duration	Treatment	Primary endpoint	Secondary endpoints
Phase 3 induction and maintenance study with a treat-through design (ELEVATE UC 52) (Fig. 2) ³³	Multicentre, phase 3, randomised, double-blind, placebo-controlled clinical trial	433 patients with moderate to severe UC aged 16–80 who had to meet the same inclusion and exclusion criteria as the ELEVATE UC 12 study	52 weeks	289 received etrasimod 2 mg once a day and 144 placebo	Percentage of patients achieving clinical remission at week 12 and week 52	Percentage of patients achieving endoscopic improvement, symptom remission, endoscopic improvement/histological remission (EIHR), clinical response, corticosteroid-free clinical remission and sustained clinical remission
Extension study (ELEVATE UC OLE) ⁵⁸	Phase 3, multicentre, open-label, uncontrolled, extension study of patients with moderate to severe active UC who have received prior double-blinded treatment (etrasimod 2 mg once a day or placebo) during their participation in one of the phase 2 or phase 3 studies		5 years		Tolerability and safety of etrasimod in the long term; number and severity of safety measures	Percentage of patients achieving clinical remission, endoscopic improvement and clinical response, as well as improvement in total and partial MMS

MMS: modified Mayo score; UC: ulcerative colitis.

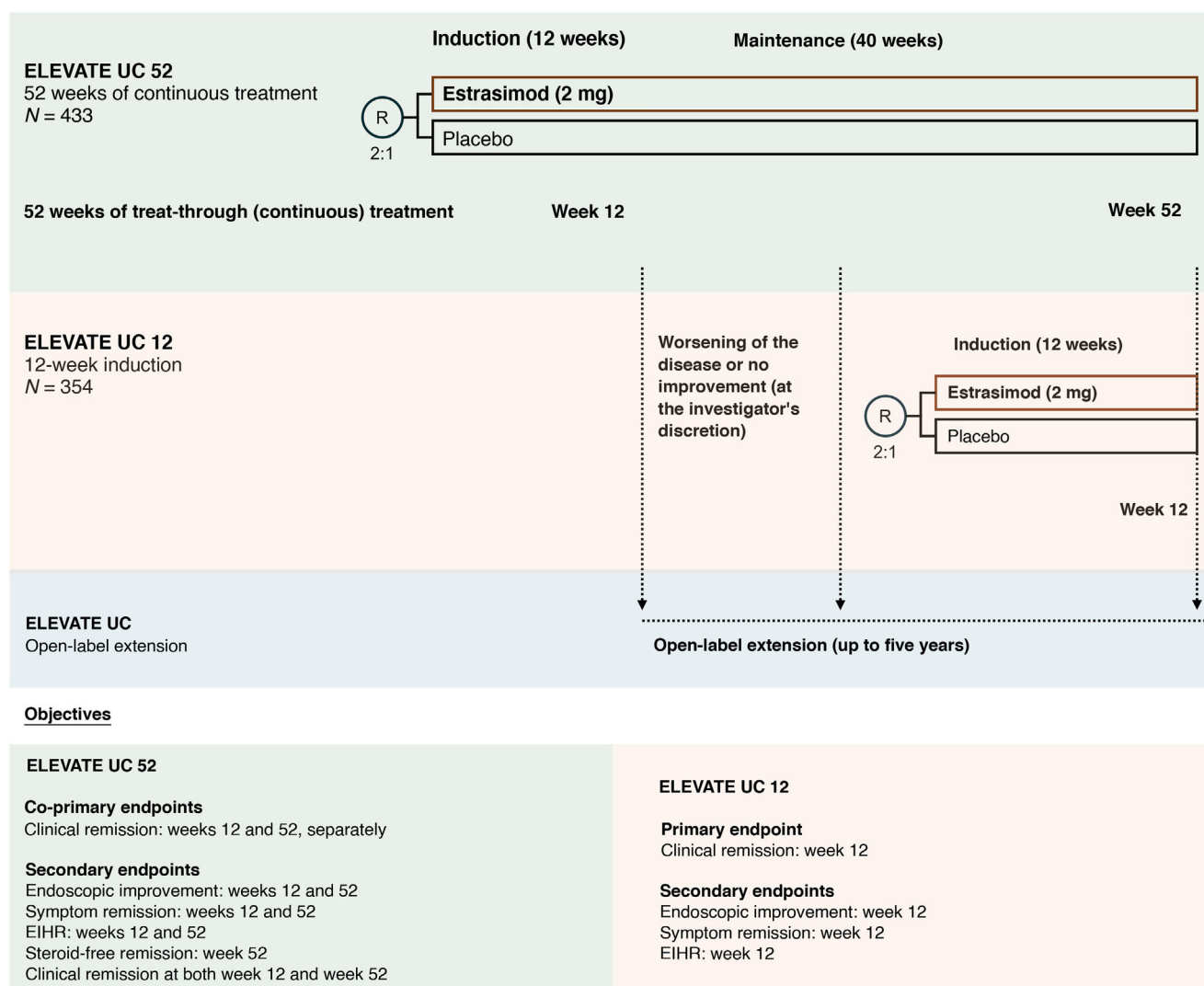


Figure 2 Clinical development of etrasimod in ulcerative colitis.³³

through (continuous) design, and the ELEVATE UC 12 study³³ (Fig. 2) are randomised, double-blind, placebo-controlled Phase 3 clinical trials. These studies included respectively 433 and 354 patients aged 16–80 with active, moderate to severe UC confirmed by endoscopy (centralised endoscopic subscore reading ≥ 2 and rectal bleeding subscore ≥ 1) and histopathology with an extent of disease ≥ 10 cm from the anal margin and a modified Mayo score (MMS) of 4–9. In addition, patients had to have experienced an inadequate response, loss of response or intolerance to at least one approved treatment for UC (oral aminosalicylates, corticosteroids, thiopurines, JAKi or biologics such as TNF, integrin or anti-IL12/23 inhibitors). In this study, patients could receive concomitant therapies for UC, such as stable daily doses of aminosalicylates or oral corticosteroids. Concomitant treatment with immunomodulators, biological therapies, rectal aminosalicylates or rectal corticosteroids was not allowed. In ELEVATE UC 52, 289 patients received 2 mg etrasimod once daily for 52 weeks, and 144 patients received placebo. Unlike studies with a design in which responders are randomised again (re-randomisation)

after the induction period, in this treat-through design study, patients assigned to each arm continued in the same arm during maintenance, without being re-randomised. In ELEVATE UC 12, 238 patients received 2 mg etrasimod once daily for 12 weeks, and 116 patients received placebo.³³

The primary endpoint was the percentage of patients achieving clinical remission (a stool frequency subscore of 0/1 with a decrease of ≥ 1 point from baseline; and a rectal bleeding subscore of 0 and endoscopic subscore ≤ 1 [no friability]) at week 12 (ELEVATE UC 52 and 12) and week 52 (ELEVATE UC 52) (Table 2). Secondary endpoints included the percentage of patients achieving endoscopic improvement, symptomatic remission and endoscopic improvement-histological remission (EIHR) at week 12 (ELEVATE UC 52 and ELEVATE UC 12), and clinical remission without corticosteroids and maintained clinical remission (ELEVATE UC 52) (Table 2). It should be noted that symptomatic remission is a demanding composite variable and is not commonly used in the assessment of efficacy of advanced therapies.³³

Table 2 Efficacy and tolerability results in clinical trials of etrasimod in patients with moderate to severe ulcerative colitis.

Study	No. of patients	Criteria	Efficacy at 12 weeks (n, %)			Efficacy at 52 weeks (n, %)			Adverse effects (%)		
			Treatment	DT ^a 95% CI		Treatment	DT ^a 95% CI				
			Etrasimod 2 mg once a day	Placebo		Etrasimod 2 mg once a day	Placebo				
			<i>n</i>			<i>n</i>					
Phase 3 induction study (ELEVATE UC 12) (Fig. 2) ³³	354	Primary Clinical remission ^b	238	116	55 (25)	17 (15)	10% (1%, 18%) ^j	—	—	—	• Infections: 11.3% (n=27) vs 12.1% (n=14)
		Secondary Endoscopic improvement ^c	—	—	68 (31)	21 (19)	12% (3%, 21%) ^j	—	—	—	• Serious infections: 0% vs 0%
		Endoscopic normalisation ^d	—	—	38 (17%)	9 (8%)	9.2% (2.3–16.2) ^l	—	—	—	• Herpes zoster: 0% vs 2% (n=2)
		Symptom remission ^e	—	—	104 (47)	33 (30)	17% (7%, 28%) ^j	—	—	—	• Sinus bradycardia: 2% (n=4) vs 0%
		Endoscopic improvement-histological remission ^f	—	—	36 (16)	10 (9)	7% (1%, 14%) ^j	—	—	—	• Bradycardia: <1% (n=1) vs 0%
		Clinical response ^g	—	—	138 (62)	46 (41)	21% (10%, 32%) ^k	—	—	—	• 1st-degree AV block: <1% (n=1) vs 0%
		<i>n</i>	289	144	—	—	—	—	—	—	• 2nd-degree AV block: 0% vs 0%
Phase 3 induction and maintenance study with a treat-through design (ELEVATE UC 52) (Fig. 2) ³³	433	Primary Clinical remission ^b	—	—	74 (27)	10 (7)	20% (13%, 27%) ^k	88 (32)	9 (7)	25% (18%, 32%) ^k	• Infections: 24.9% (n=72) vs 22.2% (n=32)
		Secondary Endoscopic improvement ^c	—	—	96 (35)	19 (14)	21% (13%, 29%) ^k	102 (37)	14 (10)	27% (19%, 34%) ^k	• Severe infections: 1% (n=3) vs 3% (n=5)
		Endoscopic normalisation ^d	—	—	40 (15%)	6 (4%)	10.2% (4.7–15.7) ^m	72 (26%)	8 (6%)	20.4% (13.8–27.0) ⁿ	• Herpes zoster: 1% (n=2) vs 0%
		Symptom remission ^e	—	—	126 (46)	29 (22)	25% (15%, 34%) ^k	119 (43)	25 (19)	25% (16%, 34%) ^k	• Sinus bradycardia: 0% vs 0%
		Endoscopic improvement-histological remission ^f	—	—	58 (21)	6 (4)	17% (11%, 23%) ^k	73 (27)	11 (8)	18% (11%, 25%) ^k	• Bradycardia: 1% (n=4) vs 0%
		Clinical response ^g	—	—	171 (62)	46 (34)	28% (19%, 38%) ^k	132 (48)	31 (23)	25% (16%, 34%) ^k	• 1st-degree AV block: <1% (n=1) vs 0%
		Corticosteroid-free clinical remission ^h	—	—	—	—	—	88 (32)	9 (7)	25% (18%, 32%) ^k	• 2nd degree AV block: <1% (n=1) vs 0%
Sustained clinical remission ⁱ	—	—	—	—	—	49 (18)	3 (2)	16% (11%, 21%) ^k	• Macular oedema: <1% (n=1) vs 0%		

CI: confidence interval.

^a Treatment difference.^b Clinical remission was defined as a stool count subscore of 0 (or 1 with a decrease of ≥ 1 point from baseline), a subscore of 0 and an endoscopic subscore ≤ 1 (excluding friability).^c Endoscopic improvement was defined as an endoscopic subscore ≤ 1 (excluding friability).^d Endoscopic normalisation was defined as an endoscopic subscore = 0.^e Symptom remission was defined as a stool count subscore of 0 (or 1 with a decrease of ≥ 1 point from baseline) and a rectal bleeding subscore of 0.^f Endoscopic improvement-histological remission (EIHR) (also referred to as mucosal healing) was defined as an endoscopic subscore ≤ 1 (excluding friability) with histological remission (Geboes index score < 2.0 , indicating no neutrophils in epithelial crypts or lamina propria, no increase in eosinophils, and no destruction of crypts, erosions, ulcerations or granulation tissue).^g Clinical response was defined as a decrease of ≥ 2 points and $\geq 30\%$ from baseline in the modified Mayo Clinic score, and a decrease of ≥ 1 point from baseline in the rectal bleeding subscore or an absolute rectal bleeding subscore ≤ 1 .^h Corticosteroid-free clinical remission was defined as clinical remission at week 52 without receiving corticosteroids for at least 12 weeks prior to week 52.ⁱ Sustained clinical remission was defined as clinical remission at both week 12 and week 52.^j $p < 0.05$.^k $p < 0.001$.^l $p < 0.0093$.^m $p < 0.0027$.ⁿ $p < 0.0001$.

Efficacy of etrasimod in patients with ulcerative colitis in the ELEVATE studies

Demographic data

The patients included had similar baseline clinical and demographic characteristics in the two treatment groups. The mean disease duration was seven years, 33% had pancolitis, 60% had left colitis, 7% had isolated ulcerative proctitis and the mean MMS score was 7.³⁵ Thirty percent of patients in ELEVATE UC 52 and 33% in ELEVATE UC 12 had previously received biologics or JAKi, and 33% in both studies were receiving corticosteroids at baseline.³³

Clinical efficacy

Phase 3 clinical trials confirmed the superiority of etrasimod over placebo in induction therapy at 12 weeks and maintenance of clinical remission until week 52 in patients with moderate to severe UC (Table 2).

Effectiveness of induction treatment at 12 weeks

In the ELEVATE UC 52 study, a significantly higher proportion of patients in the etrasimod 2 mg once daily group achieved clinical remission compared to patients in the placebo group at the end of the 12-week induction period (27% vs 7%; $p < 0.0001$). Statistically significant differences were also found with etrasimod versus placebo on criteria such as endoscopic improvement (35% vs 14%), endoscopic normalisation (15% vs 4%), symptomatic remission (46% vs 21%) and EIHR (21% vs 4%)³³ (Table 2).

In the ELEVATE UC 12 study, 25% of patients in the etrasimod group achieved clinical remission compared to 15% of patients in the placebo group at the end of the 12-week induction period ($p = 0.026$). Furthermore, a statistically significant improvement was found with etrasimod 2 mg once daily compared to placebo in secondary endpoints such as endoscopic improvement (31% vs 19%), endoscopic normalisation (17% vs 8%), symptomatic remission (47% vs 30%) and EIHR (16% vs 9%)³³ (Table 2).

Rapid onset time of response to etrasimod

Rapid symptom relief was seen in both studies.³⁶ Differences between treatment groups were significant from day two for symptomatic response (decrease $\geq 30\%$ from baseline in rectal bleeding subscore/stool frequency subscore [RBS/SFS]) and from day 11 for symptomatic remission. The percentage of patients achieving remission of rectal bleeding and normalisation of stool frequency was higher in patients receiving etrasimod compared to placebo, with these differences being statistically significant from day 15 for rectal bleeding and day three for stool frequency.³⁶

Effect of etrasimod on the decrease in lymphocyte count

Consistent with etrasimod's mechanism of action, mean lymphocyte counts at week two in etrasimod-treated patients decreased by an average of 50% from baseline and remained

stable during follow-up in ELEVATE UC 52 and ELEVATE UC 12.³³ In addition, of the total patients who received etrasimod and completed either study but did not continue treatment in the open-label extension study ($n = 31$), absolute lymphocyte counts returned to normal in 83% of patients after 52 weeks of treatment in ELEVATE UC 52 and in 77% of patients after 12 weeks of treatment in ELEVATE UC 12 at two weeks after stopping treatment.³³

Efficacy of etrasimod maintenance treatment at 52 weeks

In the maintenance study (ELEVATE UC 52), a significantly higher proportion of patients in the etrasimod group achieved clinical remission compared to patients in the placebo group at the end of the 52-week follow-up period (32% vs 7%; $p < 0.0001$). The key secondary efficacy endpoints of endoscopic improvement (37% vs 10%), sustained clinical remission (18% vs 2%), symptomatic remission (43% vs 19%), EIHR (27% vs 8%) and steroid-free remission (32% vs 7%)³³ were also met (Table 2) (Fig. 3A). Lastly, all patients who achieved clinical remission at week 52 remained steroid-free for 12 weeks.

Clinical efficacy of etrasimod in the maintenance period in induction responders

A *post hoc* analysis of the ELEVATE UC 52 study analysed clinical remission, steroid-free remission, endoscopic improvement, EIHR and symptom remission at week 52 in patients with a baseline MMS of 5–9, regardless of whether or not they met clinical response criteria at week 12.²²

Among patients who responded to induction therapy at week 12, those treated with etrasimod had a higher clinical remission rate at week 52 vs placebo (49.1% vs 17.4%; $p < 0.001$), with similar results found for all other efficacy endpoints at week 52 ($p < 0.05$) (Fig. 3B). These results may help put the efficacy of etrasimod at 52 weeks into context with that of treatments that used responder randomisation designs.

Efficacy of etrasimod based on previous treatments

In the ELEVATE UC 52 trial, one third of the patients had previously been exposed to biologics or JAK inhibitors; 22% had previously received TNF inhibitors, 11% integrin inhibitors, 7% JAKi and 2% IL12/23 inhibitors.^{33,37} Similarly in ELEVATE UC 12, a third of the patients had previously been exposed to these drugs.³⁸

More patients previously exposed to a biologic/JAKi had pancolitis and an MMS of 7–9, and longer disease duration, compared to those who had not had prior treatment with these drugs (bio/JAKi-naïve patients).³⁸ The effects of etrasimod treatment were statistically and clinically significant in both groups compared to placebo in both the induction and maintenance periods, with a similar safety profile. In ELEVATE UC 52, 31% of bio/JAKi-naïve and 17% of exposed patients achieved clinical remission at week 12, compared to 10% and 2% of placebo-treated patients. At 52 weeks, clinical remission rates were 37% in the bio/JAKi-naïve group and 21% among those exposed, compared to

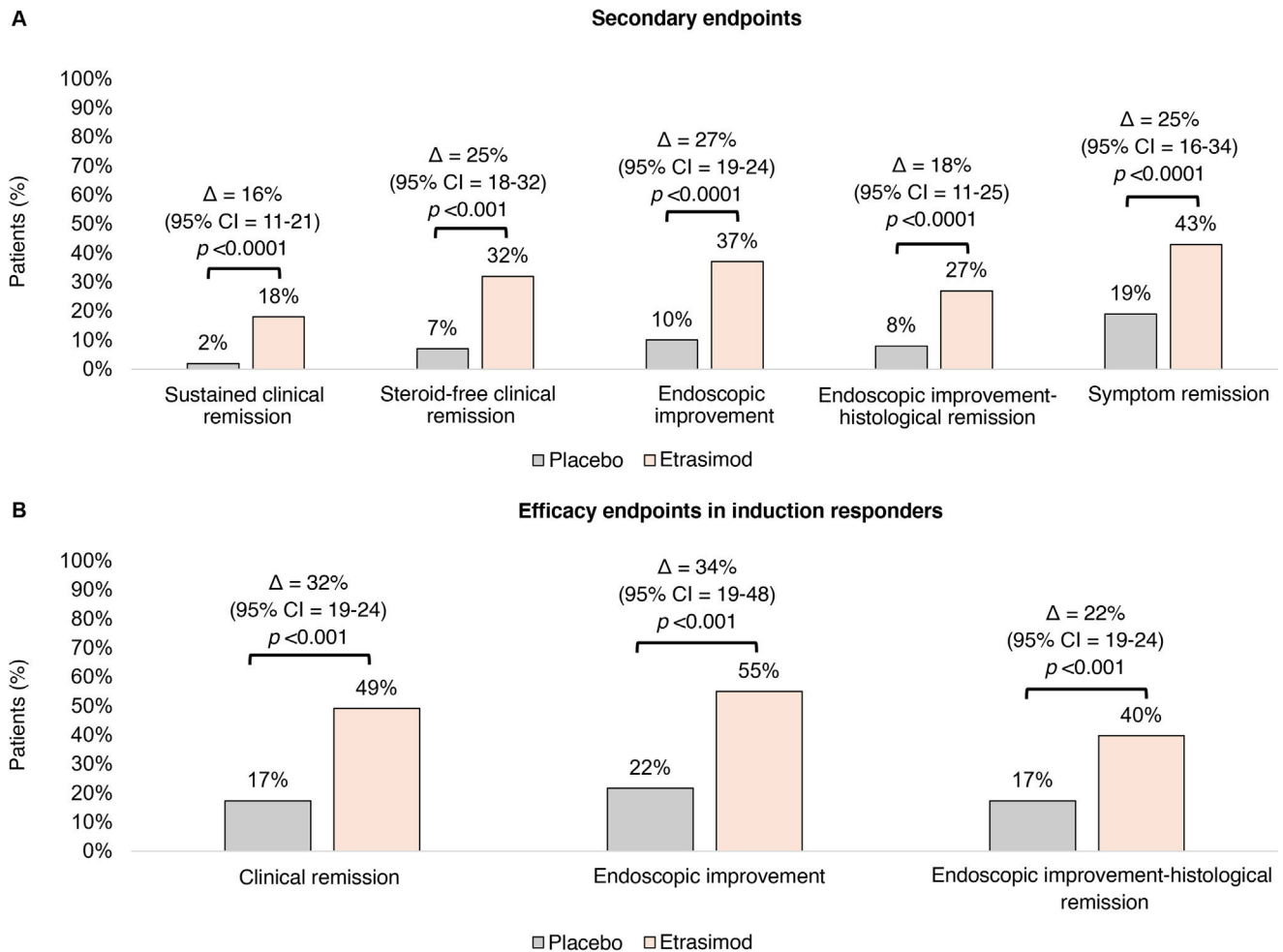


Figure 3 (A) Sustained clinical remission, corticosteroid-free clinical remission, endoscopic improvement, endoscopic improvement-histological remission and symptom remission at 52 weeks in the ELEVATE UC 52 study. (B) Efficacy of etrasimod at week 52 in patients who achieved clinical response at 12 weeks in the ELEVATE UC 52 study (responders).^{31,33} CI: confidence interval.

CI: confidence interval.

7.5% and 5% for those treated with placebo in each group. In ELEVATE UC 12, 28% of bio/JAKi-naïve patients treated with etrasimod achieved clinical remission, compared to 16% in the placebo group. Among ELEVATE UC 12 participants previously exposed to biologics/JAKi, numerical improvements were found in all efficacy variables, and statistically significant results in clinical response.³⁸

Comparing the effects of etrasimod in patients exposed to one or two or more biologics/JAKi, higher rates of clinical remission, clinical response, endoscopic improvement and clinical remission without steroids were found at week 12 and 52 in those exposed to a single biologic/JAKi.³⁸ These results are consistent with those found when other advanced therapies have been used in UC patients previously exposed to more than one biologic.³⁹

Efficacy of etrasimod in patients with isolated proctitis

The management of patients with proctitis can be difficult. They are routinely excluded from phase 3 clinical trials,

despite the fact that proctitis can have a significant negative influence on quality of life^{40,41} and patients with uncontrolled proctitis frequently develop more extensive forms of the disease.⁴²

The ELEVATE UC 52 and 12 studies allowed the inclusion of patients with isolated proctitis (with rectal involvement <10cm) provided they met all other inclusion criteria and with recruitment limited to 15%. An analysis was conducted of the 64 participants (42 and 22, receiving etrasimod and placebo respectively) with isolated proctitis at week 12 from both studies and 36 participants (27 and 9, receiving etrasimod and placebo respectively) at week 52 from the ELEVATE UC 52 study.¹⁹

At week 12, in the patients with isolated proctitis, a higher proportion treated with etrasimod compared to placebo ($p < 0.05$) achieved clinical remission (43% vs 14% respectively), endoscopic improvement (52% vs 23%), symptomatic remission (52% vs 23%), EIHR (38% vs 14%) and clinical response (71% vs 41%).⁴³

At week 52 in the ELEVATE UC 52 study, 44% and 56% of patients treated with etrasimod achieved clinical and

symptomatic remission, respectively, compared to 11% who achieved both types of remission in the placebo group.⁴³

Quality of life and outcomes reported by etrasimod-treated patients

Patients treated with etrasimod showed greater improvement from baseline in the Inflammatory Bowel Disease Questionnaire overall and in the scores for its four domains at the end of the 12-week induction phase and the 52-week maintenance phase compared to placebo. These findings demonstrate the benefits of etrasimod on disease-specific health-related quality of life and support the clinical findings of the ELEVATE programme.⁴⁴

In addition, when the earliest evaluation was carried out, etrasimod was found to have improved symptoms related to isolated proctitis, such as rectal bleeding at week two and urgency within 12 weeks of treatment.¹⁹

Differences between etrasimod and other advanced therapies

There are currently seven biologics and three JAKi which have been shown to be effective in the treatment of moderate to severe UC and are approved by the European Medicines Agency.

Biologics are monoclonal antibodies with a selective action on their target molecule. Because they are modified antibodies, they may induce some immunogenicity (mainly the TNF inhibitors),⁵ which may be related to the loss of response and thus the need for them to be combined with immunosuppressants (for example, thiopurines), with the consequent increased risk of adverse events, or the need for dose escalation.^{13,18,45,46} It is estimated that 50% of patients receiving TNF inhibitors have a loss of response over time^{47,48}; the incidence rate of loss of response with vedolizumab in patients with UC is 18–39% at 6–12 months follow-up⁴⁹ or 40% per patient-year of follow-up,⁵⁰ and lastly, at least 35% of patients treated with ustekinumab require a dose increase due to loss of response⁵¹.

JAKi, however, do not produce this immunogenicity, although they do require some dose escalation during maintenance to maintain efficacy.¹⁰ In addition, although JAKi and S1PR modulators, such as etrasimod, are currently the only advanced oral therapies available for moderate to severe UC, JAKi have a number of specific recommendations to be used only when suitable therapeutic options are not available in certain population groups.^{52–54}

Etrasimod is a small molecule (<1 kDa) rapidly absorbed after oral administration. No clinically significant differences have been detected in patients treated with etrasimod based on gender, age and body weight, so there is no indication to adjust the dose based on weight, only precaution regarding its use in patients weighing less than 40 kg.²³ Unlike biologics, etrasimod has a short half-life ($t_{1/2}$: 30 h), and its metabolism results in the production of the parent compound and non-active minor metabolites.^{23,55}

Treatment with etrasimod is started at 2 mg once daily during the induction period, without the need for titration, and is maintained at the same dose throughout the

maintenance period.³³ Like JAKi, the oral route of administration is an advantage for the patient, especially compared to biologics which require intravenous or subcutaneous administration.⁵⁶ Compared to agents requiring intravenous administration, small molecules such as etrasimod avoid the need for frequent hospital visits, offering greater convenience and flexibility for the patient. In addition, its oral administration has a positive economic impact by reducing the costs associated with scheduled visits and eliminating the need for specialised infusion staff.

Positioning of etrasimod in ulcerative colitis

Etrasimod is a new advanced therapy alternative for the treatment of patients aged 16 and over with moderate to severe active UC. Its oral administration and once-daily dosing could be associated with good patient adherence. Etrasimod acts by inhibiting the outflow of lymphocytes from the lymph nodes into the bloodstream, an effective and novel mechanism of action to reduce intestinal inflammation, as confirmed by clinical results obtained in the ELEVATE studies.³² These studies have shown that 27% of patients treated with etrasimod achieve clinical remission by week 12. In addition, etrasimod has been shown to be more effective than placebo in achieving endoscopic improvement and EIHR, as well as in achieving sustained, steroid-free clinical remission, thus consolidating its comprehensive efficacy in various aspects of UC management, like other advanced therapies. The clinical efficacy of etrasimod versus placebo has been similar in bio/JAKi-naïve patients and in those exposed to prior treatment with biologics or JAKi, both during the induction and maintenance phases, although as with other advanced therapies, the therapeutic benefit was less consistent in previously exposed patients.³³ For this reason, etrasimod could be considered as a first-line option in the treatment of moderate to severe UC.

Etrasimod has demonstrated a rapid response, with significant differences compared to placebo from day two for symptom response, day three for decrease in stool frequency, day 11 for symptom remission and day 15 for disappearance of rectal bleeding.^{33,36}

Etrasimod is the first systemic therapy for which patients with moderate to severe UC with isolated proctitis were included in its phase 3 studies, improving stool frequency and rectal bleeding at week two.¹⁹ This is relevant if we take into account that, according to data from the ENEIDA registry,⁵⁷ 18% of patients with UC have proctitis, and of these 10% are refractory to treatment with aminosalicylates and corticosteroids, requiring the administration of immunosuppressive drugs (immunomodulators, biologics or small molecules).⁵⁷

Despite all of the above, etrasimod is not without limitations, given its recent approval and the lack of published data on its effects in real-life UC, experience that we do have with other drugs. Ongoing and future studies on the efficacy and safety of etrasimod in different patient populations and with longer follow-up times will provide scientific evidence to address this limitation.

Conclusions

Results from phase 3 clinical trials of etrasimod, the ELEVATE UC trials, have conclusively demonstrated its superiority over placebo in both induction and maintenance of clinical remission in patients with moderate to severe active UC. Moreover, they have shown significant benefits in such important aspects as endoscopic improvement, symptom remission, EIHR and corticosteroid-free remission. These findings have proven to be applicable to different patient subpopulations, and are particularly promising in groups which can be most challenging in clinical practice, such as patients previously exposed to biologics/JAKi or those with isolated proctitis (a condition frequently excluded from clinical trials, whose symptom burden profoundly affects patients' quality of life). Oral administration of etrasimod has an advantage over other therapies for UC, which may ultimately improve adherence to treatment and reduce the need for scheduled visits and for specialised infusion staff. Last of all, the efficacy of etrasimod is not affected by immunogenicity, a common limitation of the available biologics. In view of the above, etrasimod has a number of features that differentiate it from other advanced therapies and make it an innovative and attractive therapeutic option for the treatment of patients with moderate to severe UC.

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